A review of recent progress (2002-2012) on the biological activities of pyrazoles

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Dedicated to Professor Rosa M. Claramunt on the occasion of her 65th anniversary

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Abstract

In this review, we report the structures of 243 pyrazoles with their corresponding biological activities. All of them are represented around the common structure of the pyrazole ring even in those cases where the heterocycle is only a minor part of the molecule. The classification we have used is based on chemical structure considerations and not in terms of the therapeutic area which is the more common approach. Some general conclusions have been drawn linking structures with activities.

Keywords: Pyrazoles, pyrazolones, pyrazolines, medicinal chemistry ·

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1. Introduction

There are two ways to classify a family of compounds with biological properties: either based on their pharmacological activities (CNS, cardiovascular, inflammation, etc…) or on their chemical structure. Neither way avoids the problem of things belonging to two sections: very similar structures having two different activities, or compounds with very different structures having similar activities.

In 2002 we published a review entitled "Pyrazoles as drugs: facts and fantasies"[1] which was written using the more traditional classification based on biological activity. Eleven years later, we feel the need to update it using the second approach. Thus, in the present review we have grouped the pyrazoles according to their chemical features and not by therapeutic areas as it is done in *Annual Reports in Medicinal Chemistry* (*Annu. Rep. Med. Chem. abbreviated as ARMC*). These reports have been used mainly, but not exclusively, as our source of information.

2. Classification criteria for selecting pyrazoles according to their chemical structure

In the present review we have used several criteria for selecting the compounds that we have included and excluded. Thus, we have excluded fused pyrazoles, like indazoles and pyrazoloazines, although this last group contains very relevant drugs like Sildenafil (a pyrazolo[4,3-*d*]pyrimidin-7-one). We have considered reduced indazoles (mainly 4,5,6,7-tetrahydroindazoles, as tetramethylene pyrazoles) as well as other derivatives like their aza derivatives, dihydroindazoles, etc… (i.e. we have not used their systematic names but the pyrazole ring as criteria of selection).

We have considered situations where the functional group is separated from the pyrazole ring by a methylene because in amino acids the functional groups NH_2 and CO_2H are separated by a CHR. We have also included the cases where CH=CH or C≡C are spacers. All other cases, where the functional group is far from the pyrazole ring, have been classified taking into account the closest atoms.

This leads to the contents list at the beginning of this review.

When there are two or more functional groups, which is often the case, the product will be classified according to the group which appears first in the Table except for Sections 13 and 14. The last section refers to compounds bearing fluorinated substituents like F, CF_3, CH_2F, C_6F_5 and C_6F_4 directly attached to the pyrazole ring.

Within each group, the therapeutic fields will appear in the following order: Central Nervous System (CNS), pharmacodynamics, metabolic diseases and chemotherapeutic agents.[1]

Concerning references we have quoted the journals provided in *ARMC*. In cases of patents or communications to symposia we will refer to the corresponding *ARMC* volume, where the original citation can be found.

Tautomeric NH-pyrazoles are represented in a form that appears to us as the most probable,[2,3] but that should not be considered as definitive, to avoid repetition of the errors related to the pair of bases in the determination of the structure of DNA.[4,5]

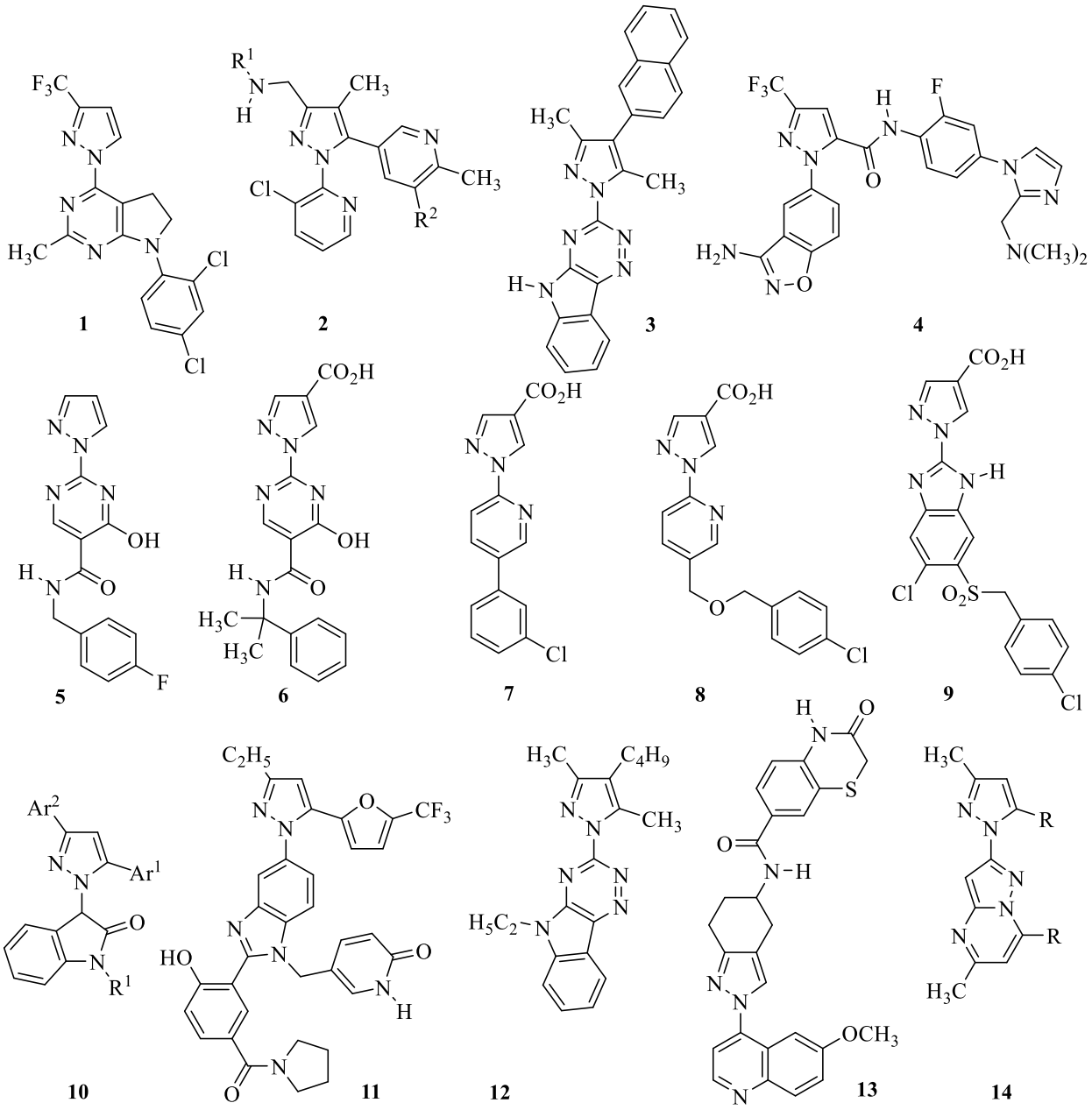
3. Heterocycles

This group includes many compounds but it is the frailest because it is arbitrary to define the pyrazole as the main group and the heterocycle as a substituent, or the other way around.

3.1 *N*-substituted compounds

The structures of some pyrazoles belonging to this section are reported in Scheme 1. Compound **2** is described under heading 3.2.1 and compounds **6**-**9** under heading 6. Compound **1** has anti-depressive and anti-anxiety properties.[6] The bipyridyl derivatives **2** (with different R^1 and R^2

substituents) are antagonists of the opioid receptor-like 1 (ORL1).[7] ORL1 was discovered in 1994, based on its high degree of amino acid sequence homology to the classical opioid receptors. Despite this homology, the classical opioids did not bind to this receptor with significant affinity. Subsequently, its endogenous agonist, a 17-amino acid peptide known as Nociceptin or Orphanin FQ (NC/OFQ), was identified. A number of reports have since demonstrated the possible involvement of the NC/OFQ-ORL1 system in pain regulation, morphine tolerance, learning and memory, food intake, anxiety, the cardiovascular system and locomotor activity. The triazacarbazole derivative **3** has been described as a BACE (β-secretase) inhibitor useful for the treatment of Alzheimer´s disease.[8]



Scheme 1. *N*-Heteroarylpyrazoles.

Razaxaban **4** (DPC906) is a factor Xa inhibitor useful as an anticoagulant.[9] Compound **5** and (mainly) the 4-carboxylic acid derivatives **6**-**9** are inhibitors of the HIF (hypoxia inducible factor) studied as possible treatments of anemia.[10-13]

The indolin-2-one derivatives **10** (15 compounds) have been reported as anti-tumor agents.[14] The complex structure **11** with five different heterocycles showed anti HIV-1 properties due to the fact that it is a CA_{NTD} (Capsid Assembly N-terminal) inhibitor.[15] Structurally related to **3**, compound **12** is an inhibitor of the HCV (hepatitis C virus) NS4B replication factor.[16] Compound **13** was shown to inhibit DNA gyrase and topoisomerase IV in *S. aureus*, *S. pneumoniae* and *E. coli* being an interesting anti-bacterial agent.[17] A series of simple pyrazolo[1,5-*a*]pyrimidines **14** (R = CH_3, aryl, thienyl) have been evaluated as anti-bacterial agents.[18]

It is difficult to reach any conclusion concerning these compounds because it is not easy to differentiate the relative influence of both heterocycles. The simplest answer is to consider that the heterocycle bearing more substituents is the core structure and the one with less, the peripheral "decoration".

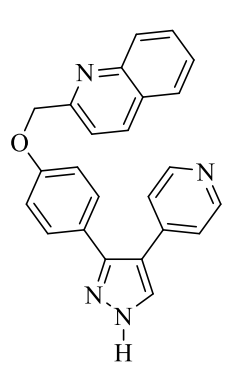
3.2 *C*-substituted compounds

3.2.1 Directly linked. This is one of the most populated sections. The structures are gathered in Schemes 2 and 3 (cancer). Compounds **15**-**22** have potential CNS applications: two PDE10 (Phosphodiesterase type II) inhibitors, **15** and **16**, for schizophrenia;[19,20] one histamine H_3 antagonist **17** (A-688057) for cognitive disorders;[21] an antipsychotic **18**;[22] a series of labeled compounds (^{11}C, ^{18}F) **19** for PET (positron emission tomography) tracers to study phosphodiesterase-10, a useful target in various CNS disorders [with R^1 an azine and R^2 a $(CH_2)_nCH_2{}^{18}F$ chain];[23-26] compound **20**, an inhibitor of c-Jun *N*-terminal kinase (JNK_3) also interesting for the treatment of CNS disorders.[27] Two compounds **21** and **22** were prepared for the treatment of Parkinson's disease which are positive allosteric modulators of mGlu4 receptor (metabotropic glutamate receptors).[28]

Anti-inflammatory derivatives **23** [inhibitor of the ERK (extracellular signal-regulated protein kinase) pathway][29] and **24** (inhibitor of the tyrosine kinase receptor)[30] have been reported. Based on the structure of Rimonabant (**99**, Section 4.3) a series of *N*-arylpyrazoles and *N*-heteroarylpyrazoles were prepared and studied as anti-obesity agents: **25** and **26** (CB1 antagonists);[31] compound **27** (CRX 000143) has a different mechanism of action being a PPARγ (peroxisome proliferator-activated receptor) modulator reducing adipogenicity;[32] compound **28** acts on the NHR LXR receptors (Nuclear hormone receptor; Liver X receptor) interfering with the lipid metabolism (we have preferred to classify this compound here instead of in Section 3.a, together with other anti-obesity compounds);[33] finally, trimethylenepyrazole **29** with a tetrazole substituent as a bioisoster of the carboxylic acid (Section 6) is a GPR109a (G-protein-coupled receptor for niacin) agonist that acts on adipocytes.[34] An insulin sensitizer **30** for the treatment of

Type 2 diabetes has been reported.[35-37] Amongst these compounds, the most interesting is **29** (MK-0354) which has been the subject of many studies and structural modifications.[38-40]

A compound for the treatment of ischemic stroke, **31** (a potent pan-JNK inhibitor)[41] and an inhibitor of coagulation to treat thromboembolic disorders **32** (inhibitor of factors IXa and XIa)[42] have been reported. Compound **33** that increases testosterone levels in male rats is a LHR (Gonadotropin luteinizing hormone) agonist.[43] For pulmonary diseases like asthma, compound **34** (MRE 2029-F20) an A_{2B} adenosine receptor antagonist[44] was studied. Derivative **35**, a MR (Mineralocorticoid receptor) antagonist has been evaluated to treat hypertension.[45]



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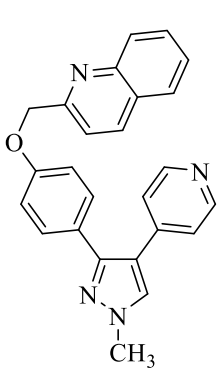

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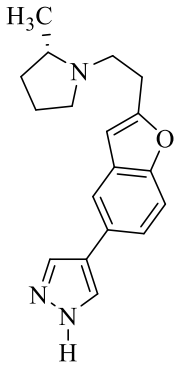

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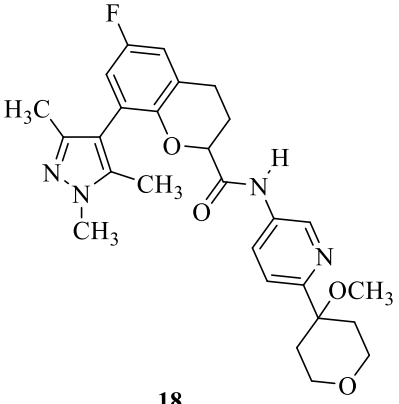

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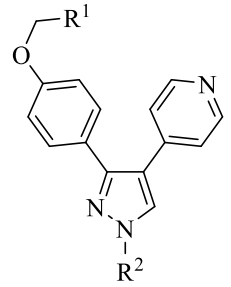

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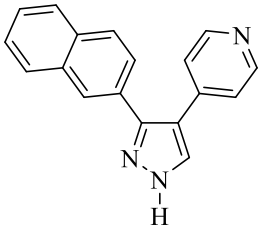

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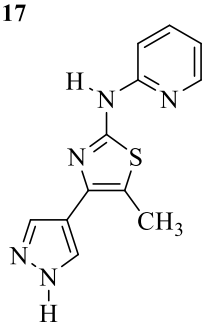

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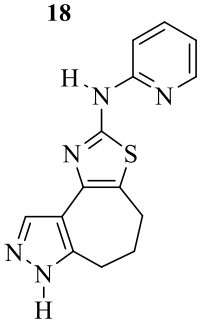

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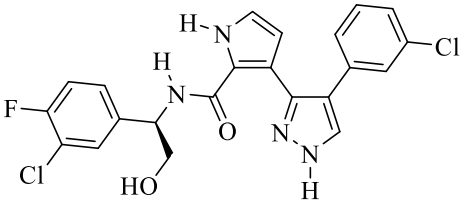

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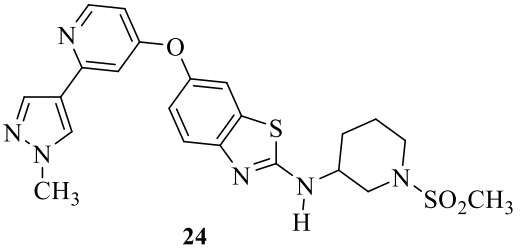

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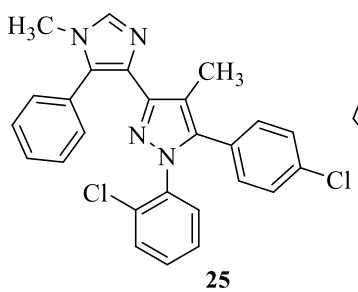

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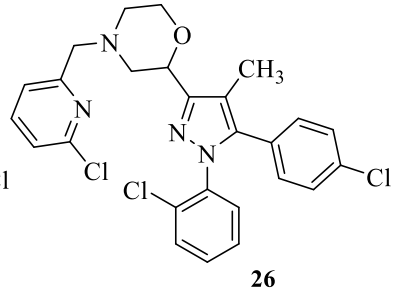

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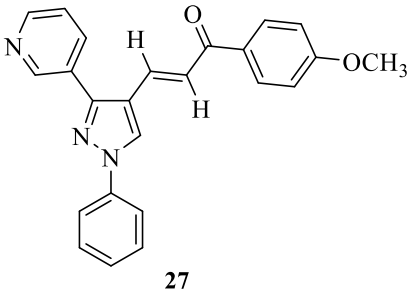

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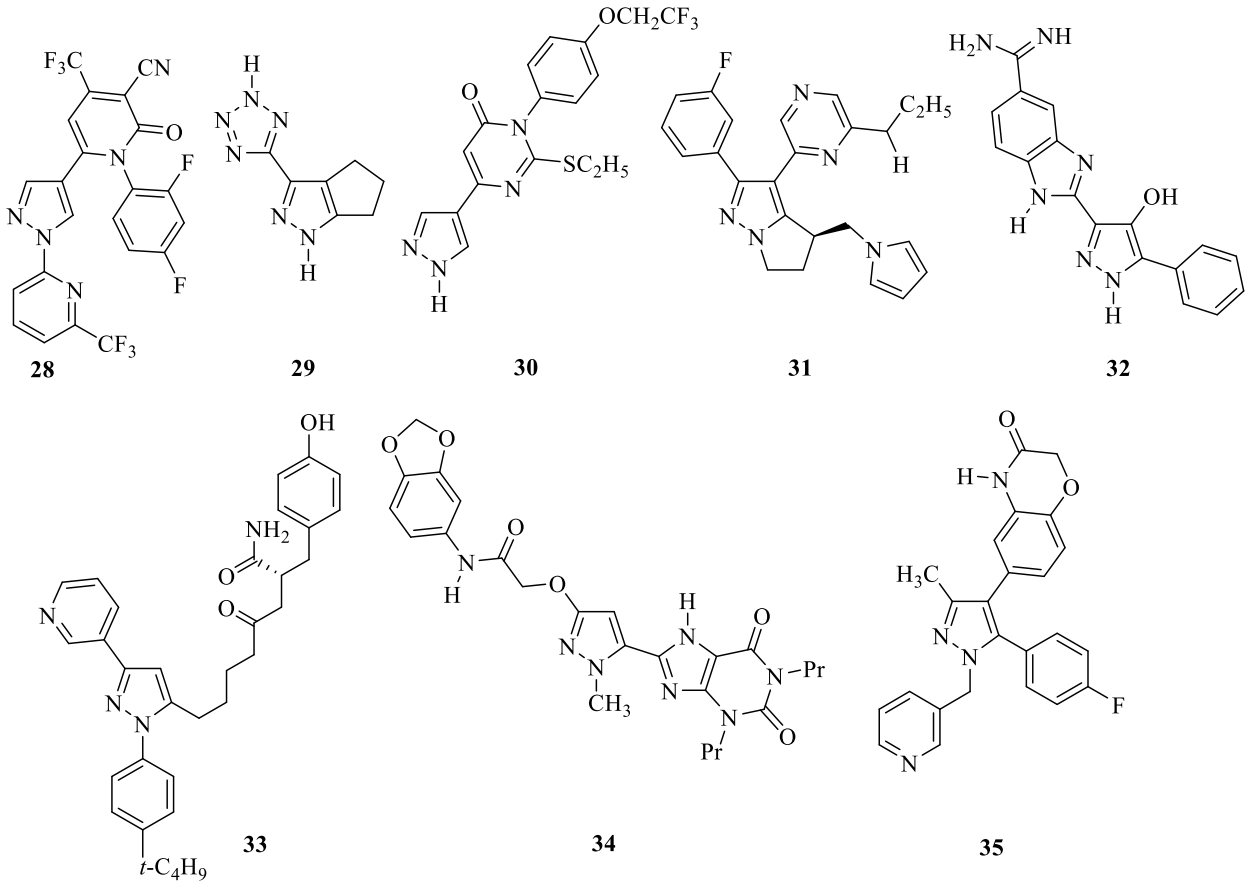
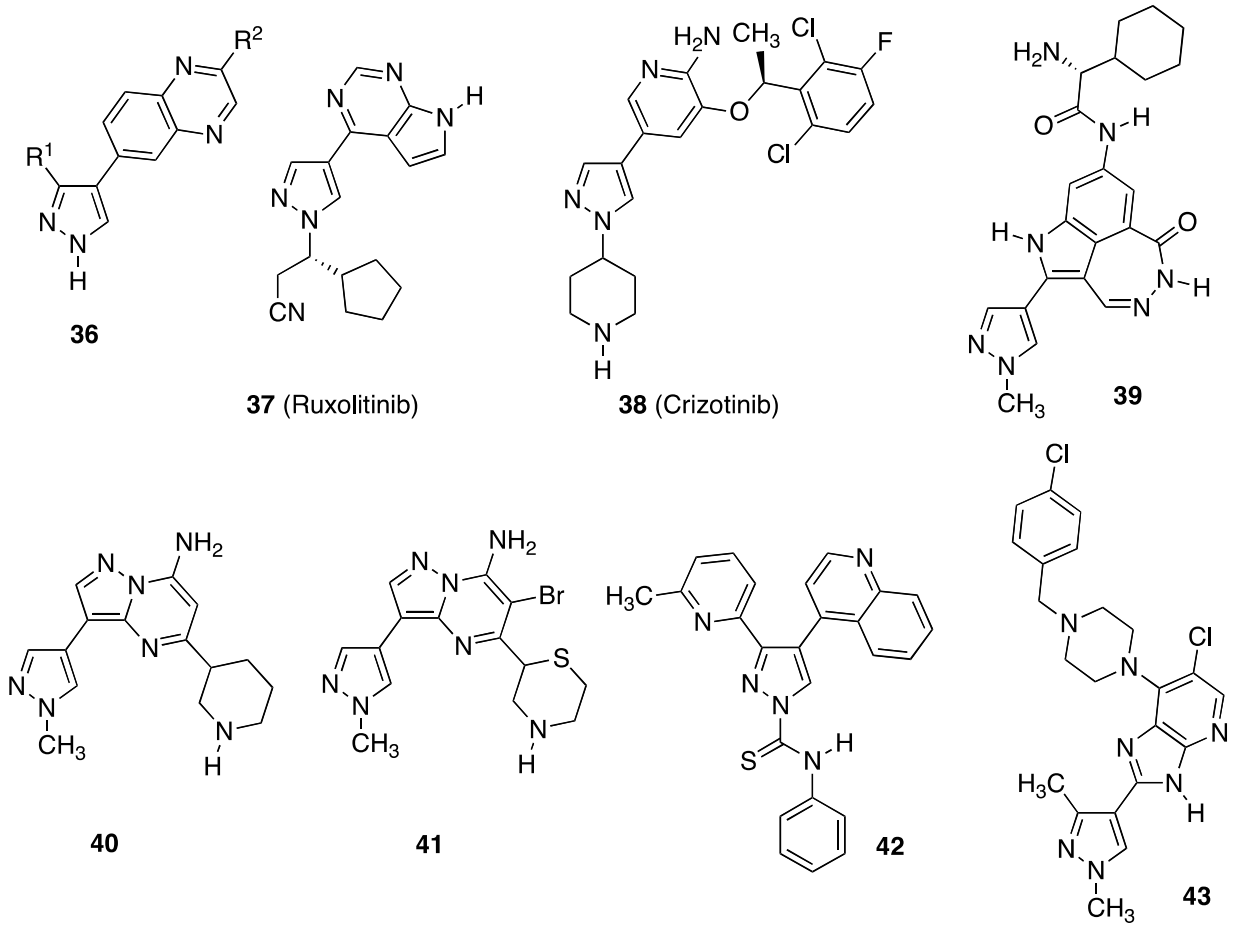


Scheme 2. *C*-heteroaryl pyrazoles.

The most important activity of *C*-arylpyrazoles is as anti-tumor agents (Scheme 3) with two compounds in the market, Ruxolitinib **37**[46] and Crizotinib **38**.[47] Quinoxaline derivatives **36**, inhibitors of PI3K (Phophatidyl-inositol-3-kinases) are tumor growth inhibitors.[48] Many papers have dealt with Ruxolitinib, a Janus kinase 2 (JK2) inhibitor for the treatment of MPN (myeloproliferative neoplasm)[49,50] and Crizotinib (PF-02341066) [a dual cMet/ALK inhibitor (protooncogen/anaplastic lymphoma kinase)] for the treatment of NSCLC (non-small cell lung carcinoma).[51,52] Compound **39** (PF-00477736) is an inhibitor of Check point kinase 1 (CHK1).[53] Pyrazolo[1,5-*a*]pyrimidine derivatives **40** and **41** (SCH900776) are CHK1 inhibitors that have been studied for preventing the progression of cancer.[54,55] Compound **42** (A-83-01) has been developed to prevent metastasis being an ALK-5 inhibitor (activin receptor-like kinase 5).[56] A large number of pyrazole derivatives bearing a 3*H*-imidazo[4,5-*b*]pyridine substituent have been studied, **43** being one of the most interesting. They are dual FLT3 (Fms-like tyrosine)/Aurora kinase inhibitors that are orally active against acute myeloid leukemia.[57]

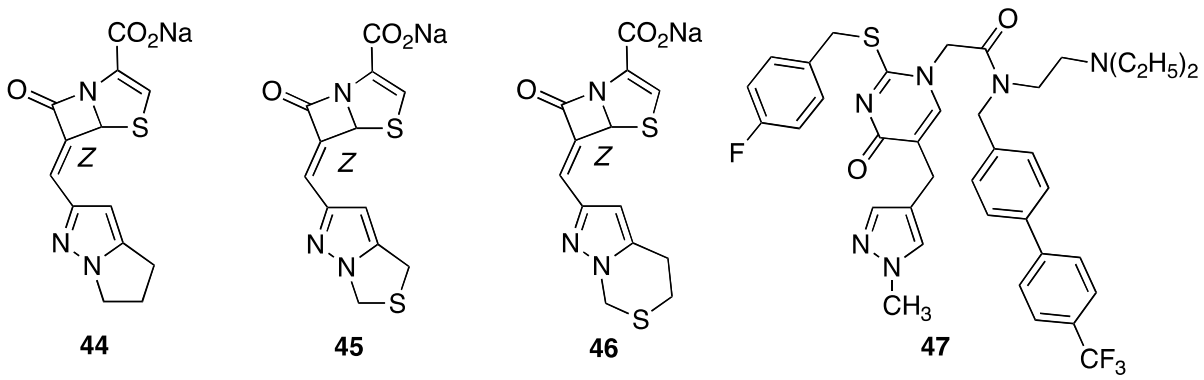


Scheme 3. *C*-heteroarylpyrazoles with anti-tumor properties.

From Section 3.2.1 it appears that often the heterocyclic substituent is on C4 and there are many NH and N-CH_3 examples except for the anti-obesity compounds that are, in general, *N*-aryl derivatives.

3.2.2 With a spacer. Only four compounds belong to this section (Scheme 4) and three of them are clearly 6-methylidene penems, the pyrazole being a substituent. They are inhibitors of β-lactamases. Compounds **44** and **45** are potent inhibitors, particularly **44**. The corresponding *E* isomer of **45** was found to be 640 times less active against TEM-1 and AmpC genes than the *Z*.[58] Penems **45** and **46** are also potent inhibitors of OXA-1 (class D) β-lactamase.[59]

Compound **47** was reported as an inhibitor of LP-PLA_2 (Lipoprotein/Phospholipase), studied for the treatment of atherosclerosis.[60,61]

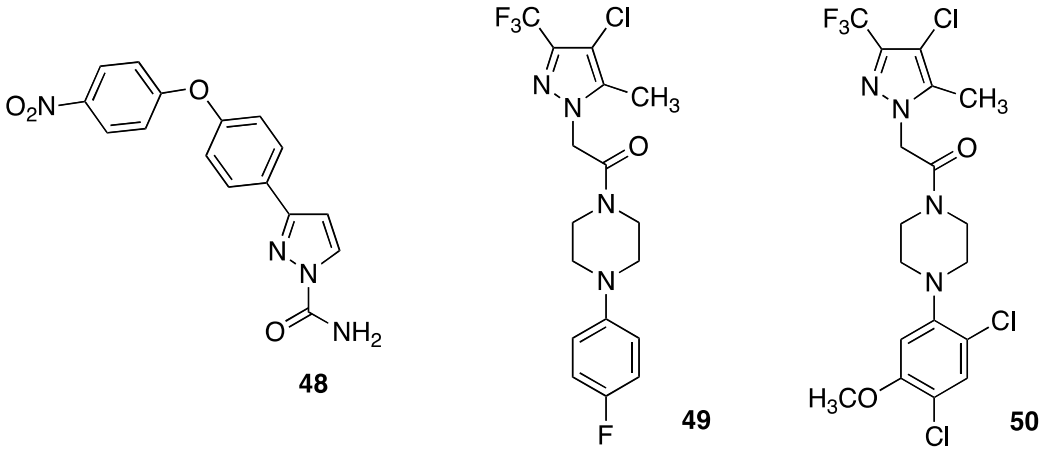


Scheme 4. *C*-heteroarylpyrazoles with a spacer.

4. Amides

4.1 *N*-substituted compounds (Pz-CO-NH-R)

4.1.1 Directly linked. Compound **48** (Scheme 5) was described as a sodium channel blocker that was studied for the treatment of neuropathic pain.[62] (Note that compound **42** of Section 3.2.1 is an *N*-thioamide).

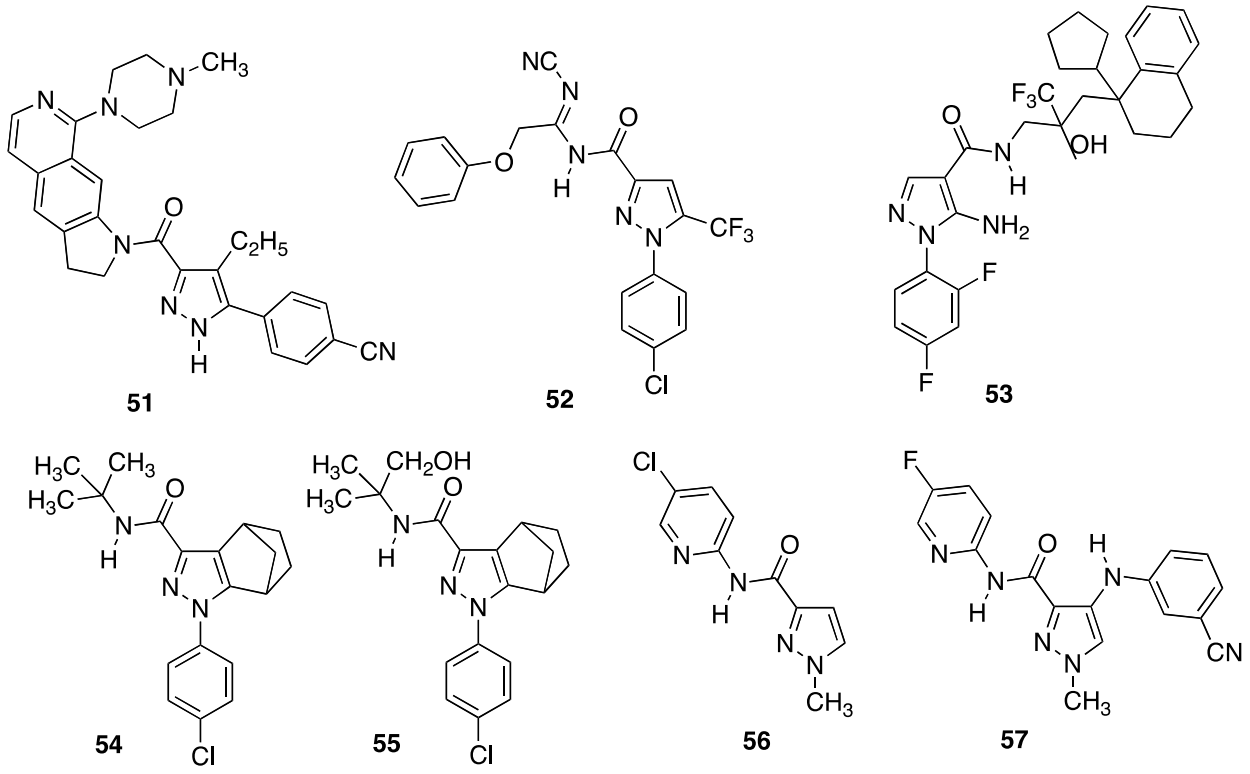


Scheme 5. *N*-substituted amides.

4.1.2 With a spacer. Compounds **49** and **50** behave as CCR1 (Chemokine receptor-1) antagonists with anti-inflammatory properties.[63]

4.2. *C*-substituted compounds

4.2.1. Pz-CO-NH-R. This Section is the one containing the most examples.

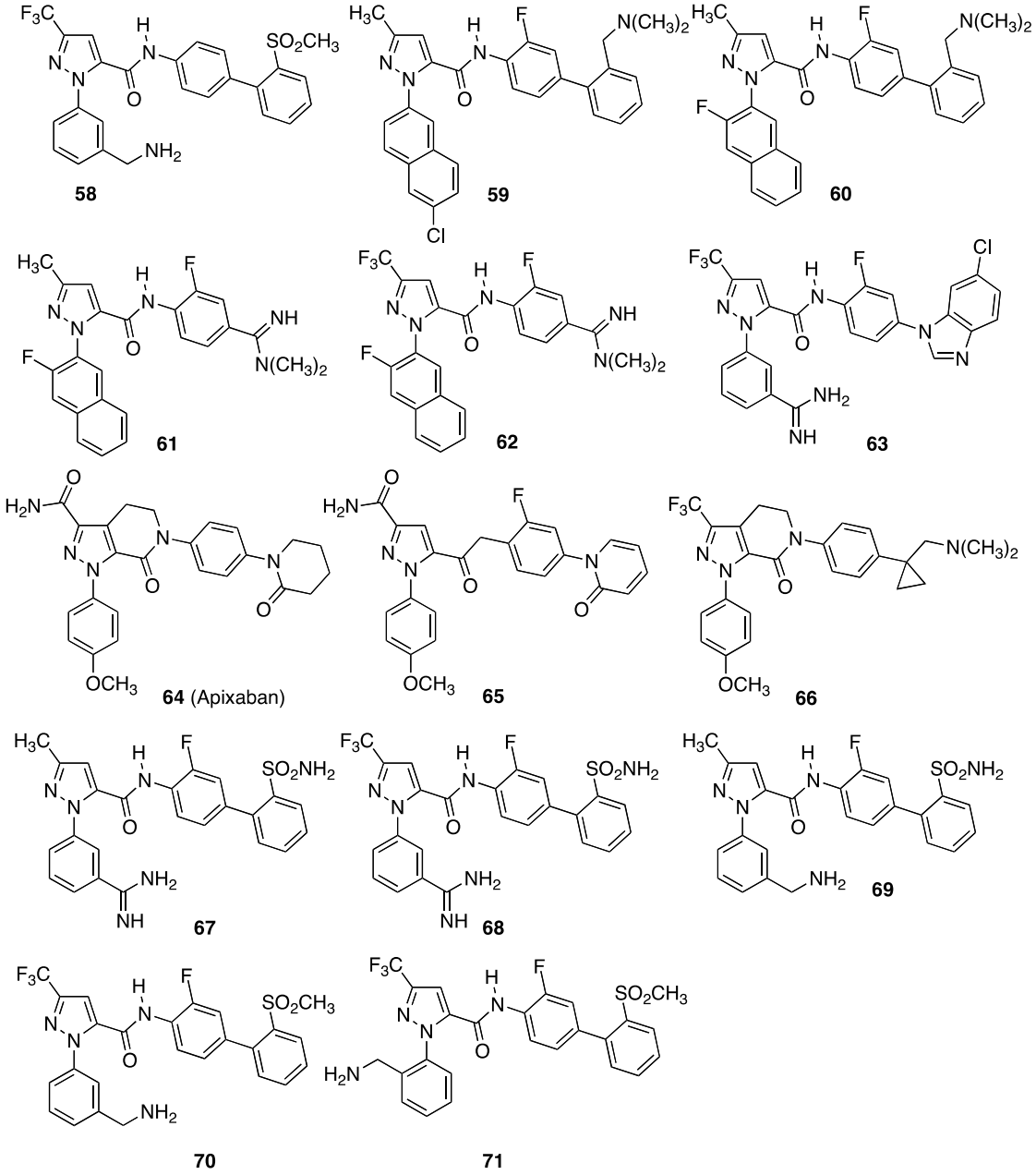


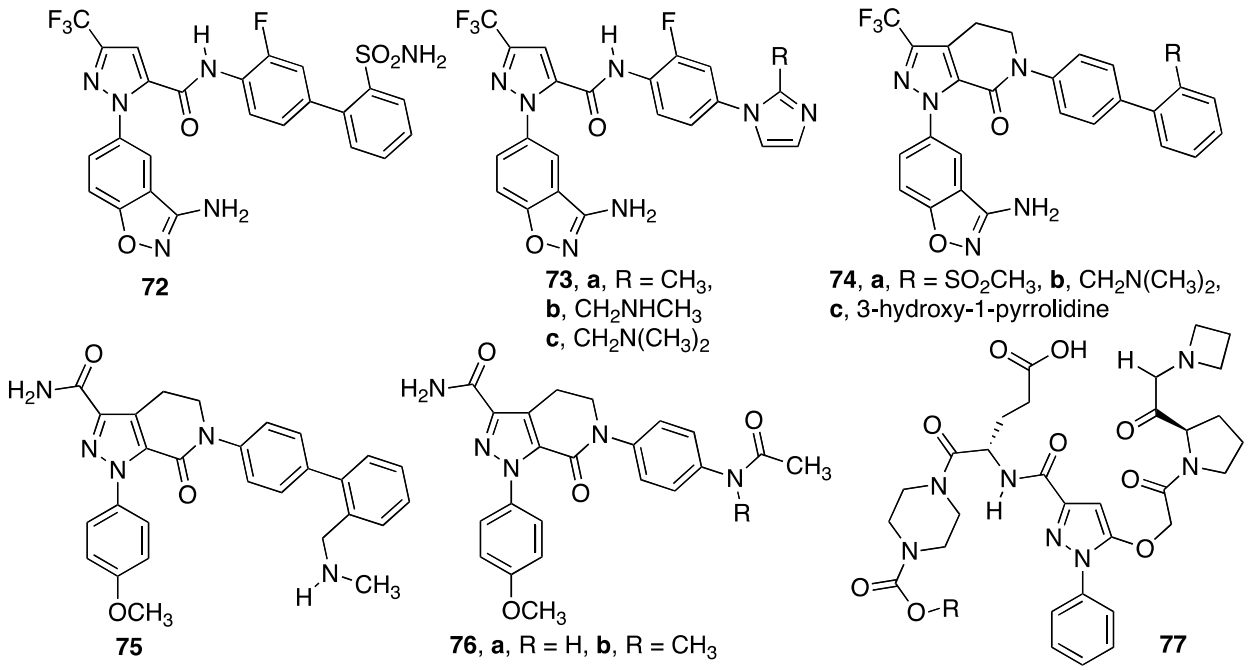
Scheme 6. CNS, pain, inflammation, Parkinson's disease.

Compound **51** showed *in vivo* 5-HT1B (5-hydroxytryptamine receptor 1B) antagonism, which makes it interesting as a potential antidepressant drug.[64] Compound **52** is a blocker of the voltage-gated sodium channel Na_v 1.8 and as such, can have application for the treatment of neuropathic pain.[65] Within a series of cannabinoid CB2 agonists, useful for inflammatory and neuropathic pain, pyrazoles **54** and **55** have been disclosed, the latter showing improved pharmacokinetic properties.[66] Methylpyrazole **56** is an activator of the potassium channel K_v7 involved in the regulation of heartbeat and neuronal activity.[67] Compound **57** has been reported as a negative allosteric modulator of mGluR5. These mGluR5 NAMs are promising agents for CNS diseases such as Parkinson´s and also for major depressive disorders.[68]

Related to Razaxaban **4**, a series of pyrazole carboxamides such as compounds **58-62** have been described as anticoagulant agents acting through inhibition of factor Xa. Among them, the trifluoromethyl derivative **62** showed an overall enhancement of pharmacokinetic properties in rat.[69,70] High throughput screening (HTS) of existing libraries was used to identify novel dual inhibitors of factor Xa and Factor IXa, another interesting target in the coagulation cascade. An example of an optimized inhibitor is benzimidazole derivative **63**.[71]

Apixaban **64** is a second-generation pyrazole-based factor Xa inhibitor which is a modification of the previous Razaxaban by constraining the pyrazole amide to a bicyclic pyrazolopyridinone. It was approved in Europe in 2011 under the trade name of Eliquis for prevention of venous thromboembolic events in patients after hip or knee replacement surgery.[72] Other pyrazole based inhibitors of factor Xa are derivatives **65** and **66**, both showing K_i in the nanomolar range. The first one, **65** was derived from Razaxaban replacing the amide linker by a ketone moiety, whereas **66** had a bicyclic core similar to that of Apixaban.[73,74] In the course of the search of Razaxaban, many pyrazole compounds have been synthesized and evaluated as Xa inhibitors, one of the first important derivatives was compound **67** (SN429) with picomolar affinity.[75]





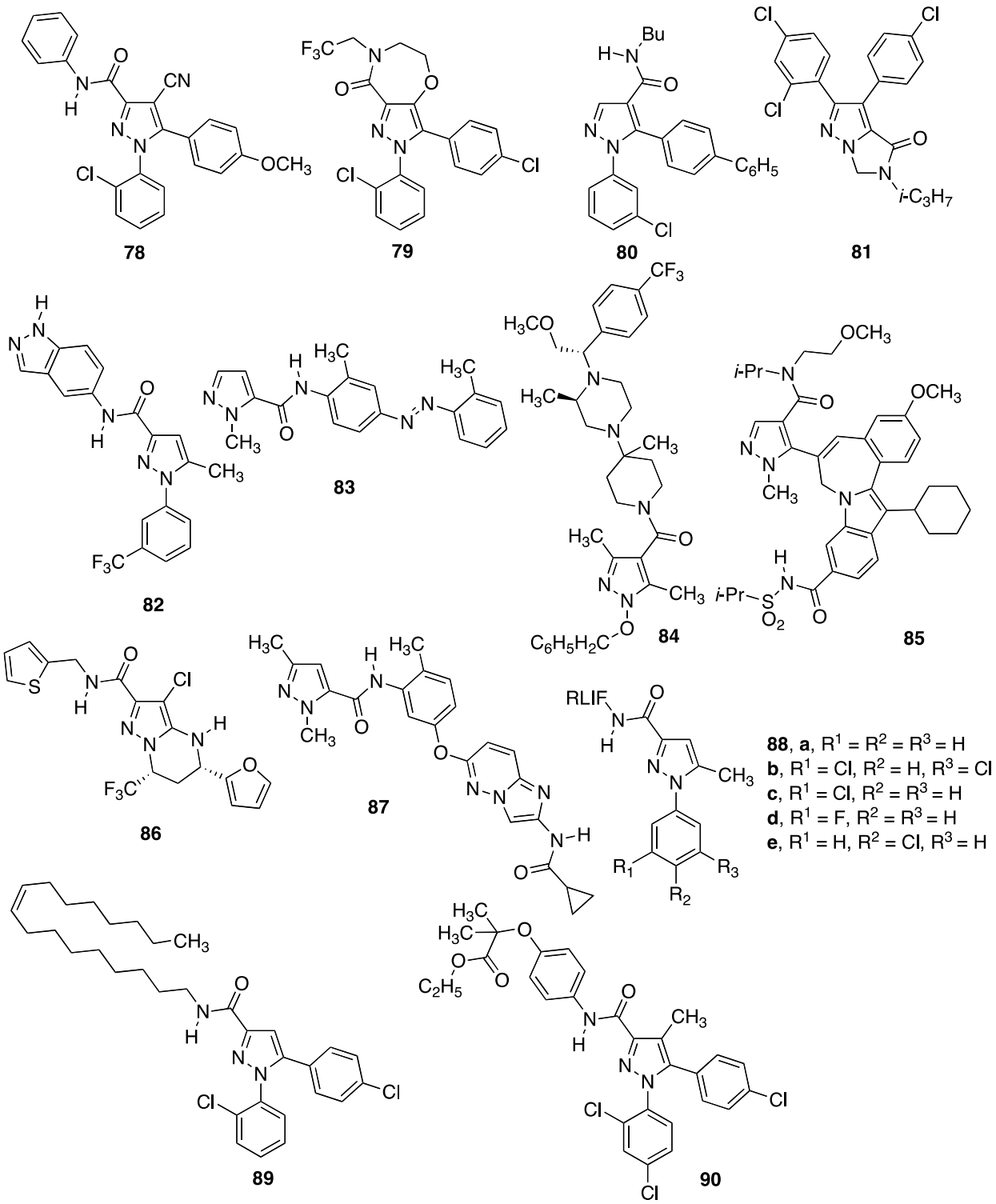
Scheme 7. Platelet anticoagulants.

Replacement of the methyl by a trifluoromethyl group afforded the very potent derivative **68**. Successful substitution of benzamidine by benzylamine as in compounds **69-71** provided the early clinical candidate **70**. In order to improve potency and selectivity the aminobenzisoxazole derivatives **72-74** were prepared. Later, and in order to avoid metabolic cleavage of the amide, rigid pyrazole scaffolds, such as dihydropyrazolopyridones **75-76** were studied.[76]

Compound **77** is the only CONHR derivative of Scheme 7 where the amide group is at position 3. It was identified as a high-affinity $P2Y_{12}$ (purinoreceptor) antagonist with interesting properties as platelet aggregation inhibitor.[77]

The pyrazole ring has been extensively studied as a structural motif in cannabinoid ligands with potential therapeutic applications in different areas. Concerning CB1 antagonists, cyano pyrazole **78**, CP-272,871 has been reported.[78] Other analogs of Rimonabant include the butyl derivative **80**[79] and conformationally constrained analogs such as **79** and 5,5 bicyclic derivatives as **81**, the latter showing the higher affinity for the cannabinoid CB1 receptor.[80]

JAK3 is an important target in immunological disorders. In a report dealing with virtual screening to identify JAK3 inhibitors, indazole **82** was described. Although it had an IC_{50} of 2.5 it did not represent an improvement over the starting compound.[81] Pyrazole **83**, CH-223191 is a potent antagonist of dioxin-induced aryl hydrocarbon receptor (AhR) in mice, and may be useful for the prevention of TCDD (2,3,7,8-Tetrachlorodibenzo-*p*-dioxin) associated pathology. TCDD is a widespread environmental pollutant with toxic effects such as endocrine disruption, immunotoxicity and liver damage.[82,83]



Scheme 8. CB1, obesity, autoimmune, antiviral, osteoporosis, antiviral, anticancer activities.

Within the antiviral field, in a patent dealing with of CXCR4 (chemokine receptor type 4) inhibitors, pyrazole **84** has been described with an IC_{50} of 0.4 nM for HIV replication. CXCR4 is

a member of the chemokine receptor family, an important target for AIDS. Compounds **85**[84] and **86** have been claimed in patents as inhibitors of HCV replication.[85]

A novel inhibitor of the vascular endothelial growth factor receptor/platelet-derived growth factor receptor (VEGFR/PDGFR) is pyrazole **87** (TAK-593) which showed a long residence time.[86]

In relation to the development of non-ATP-competitive protein kinase inhibitors for oncology, a series of pyrazoles **88a-88e** have been reported. Among them, **88c** was the most potent in the cyclin-dependent kinase, CDK2/cyclin context.[87]

Fatty acid amide derivatives of pyrazoles, such as **89**[88] have been prepared which reduce food intake *in vivo*. Designed multiple ligands targeting both the CB and the PPAR receptors have been reported. Derivatives of rimonabant linked to fibrates **90**[89] have been synthesized and the compounds have shown affinity in the nanomolar range for both types of receptors.

4.2.2 R-CO-NH-Pz. Neuropeptide Y (NPY) is an attractive target for obesity. Aryl pyrazole derivatives **91** and **92** were synthesized and evaluated as NPY Y5 antagonists. The chiral compound (–)-**91** showed good binding affinity and inhibited food intake.[90] Compound **93** (CDPPB) is a mGluR5 enhancer which reduces amphetamine-induced locomotor activity and so, of potential use for the treatment of schizophrenia.[91]

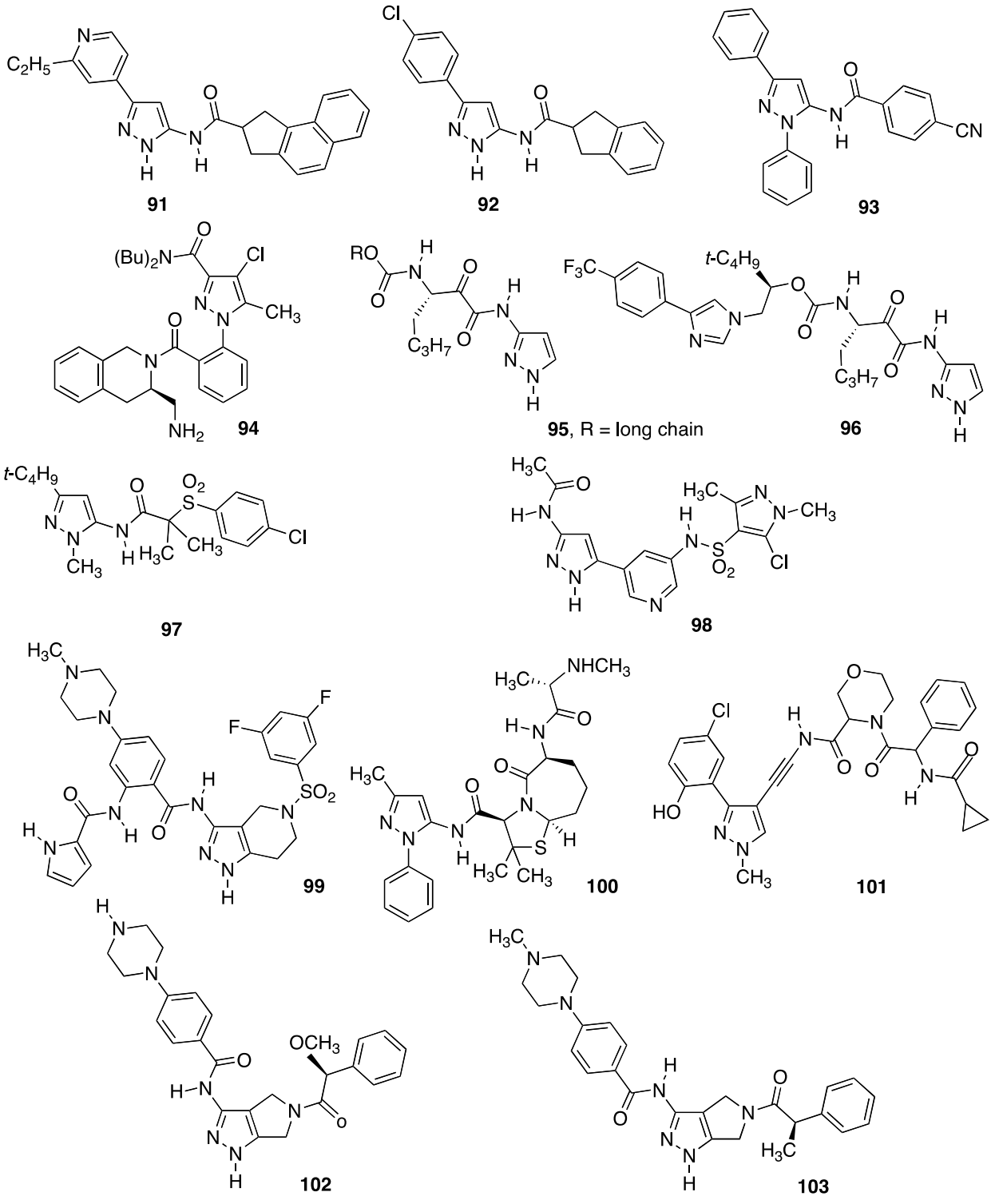
Phenylpyrazole **94** was discovered in an HTS approach as a dual BcL-2/ BcL-xL inhibitor, proteins of the BcL (B-cell Lymphoma) family which regulates apoptosis.[92] Dipeptide derivatives **95**[93,94] and **96**[95] have been disclosed as Cathepsin K (Cat K) inhibitors potentially useful for the treatment of osteoporosis. They are potent inhibitors but have poor selectivity over off-target cathepsins.

The cannabinoid CB2 receptor is a promising therapeutic target for pain devoid of the psychotropic effects associated to CB1 activation. Arylsulfone **97** showed good potency and selectivity for the cannabinoid CB2 receptor and had good pharmacokinetic properties.[96]

Pyrazole **98** was disclosed in a patent as a mixed inhibitor of mTOR (mammalian target of rapamycin) and PI3K (phosphatidylinositol-3-OH kinase) potentially useful in oncology.[97] Insulin-Like Growth Factor-1 Receptor (IGF-1R) is an emerging cell signaling pathway currently explored for cancer therapy. In a patent dealing with bicyclic pyrazole inhibitors of IGF-1R, the most potent compound was **99**, although with limited activity.[98] Penicillamine-derived analog **100** was designed as a Smac (second mitochondrial activator of caspases) mimetic which may have potential use in cancer therapeutics.[99]

Acetylene derivative **101** belongs to the first generation of NS5A (Nonstructural Protein 5A) inhibitors. Novel compounds targeting NS5A are in clinical development as an approach to treat HCV.[100] Pyrrolidinopyrazole **102** (PHA-739358) is a potent aurora kinase inhibitor with an antitumor profile.[101] Compound **103** (PHA-E429) is a PARP (poly [ADP-ribose] polymerase) inhibitor, a promising strategy for cancer treatment.[102-104]

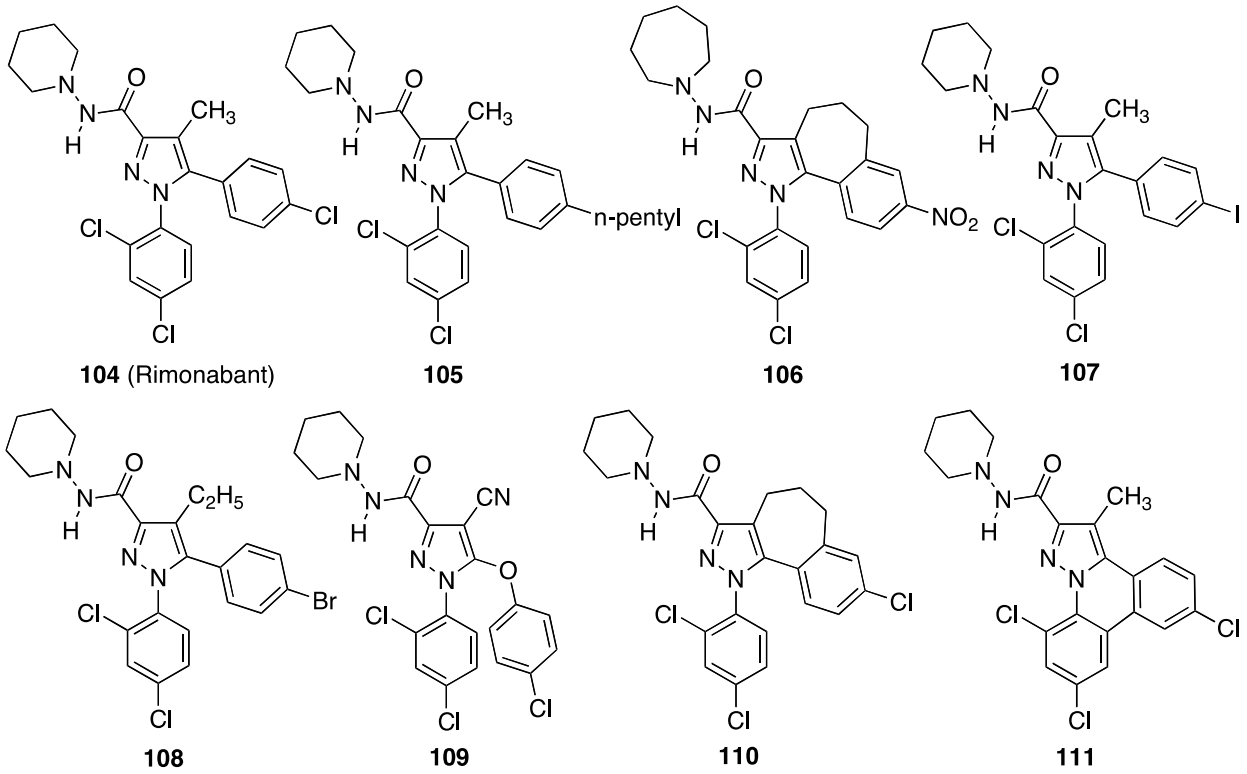
Note that compounds **91** and **98** belong also to Section 3.2.1.



Scheme 9. Amides derived from aminopyrazoles.

4.3. Hydrazides

Many diaryl pyrazoles have been synthesized and evaluated as CB1 ligands, the most important being Rimonabant **104**, which was launched as anti-obesity agent in Europe in 2006, and withdrawn from the market in 2007 due to side effects.

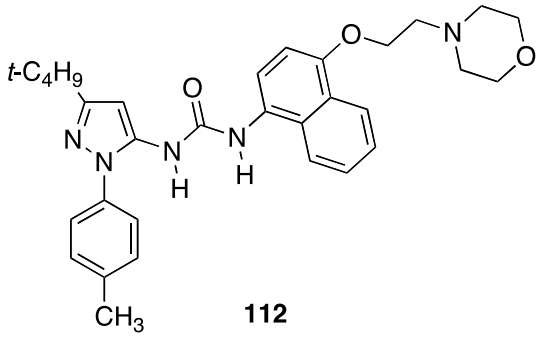


Scheme 10. Rimonabant (**104**) and related pyrazoles.

A large number of analogues have been described in which all the substituents have been modified: the methyl at C-4, the aromatic rings and their substituents, and the piperidine which has been substituted by other rings and by alkyl chains.[105-107]
Worth mentioning are **105** (OL-1302) with a pentyl chain at the phenyl ring,[108] **107** (AM251) obtained by replacing the 5-phenyl chloro substituent by iodine which is used as a reference compound in cannabinoid studies,[109] and **108** (SR147778) which reduced food intake in rats.[110] Besides, different groups have reported conformationally restricted analogs of Rimonabant such as **106**,[111] **110** with nanomolar affinity for the hCB1 receptor,[112] referred also as NESS0327 in another publication[113] and **111**.[31] A patent has been filed for the 5-aryloxypyrazole **109**, a CB1 antagonist.[31]

4.4. Ureas

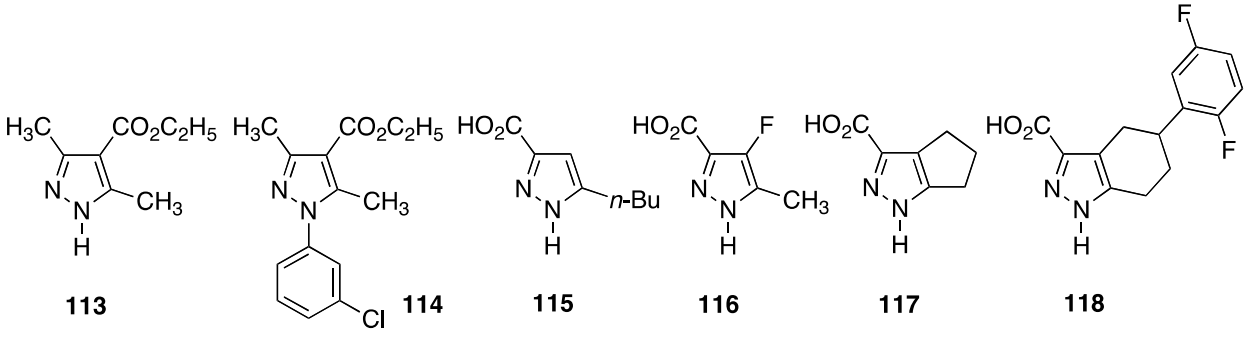
We have found only one urea derivative, **112** (Doramapimod) investigated as a possible treatment for rheumatoid arthritis.[114,115]



112

5. Esters

There are very few examples of pyrazole esters (Scheme 11).



113 **114** **115** **116** **117** **118**

Scheme 11. Pyrazole esters and carboxylic acids.

A library of about 20,000 ‘‘scaffold’’ compounds with molecular weights of 125–350 Da was screened in a combination of biochemical assays and crystallography studies to identify the PDE4 inhibitor pyrazole ester derivative **113**.[116] A 4000-fold increase in potency was achieved after only two rounds of chemical synthesis to give **114**. These compounds were designed for the treatment of asthma.

6. Carboxylic acids

Three pyrazole-3-carboxylic acids are depicted in Scheme 11. A series of pyrazole-3-carboxylic acids has been reported as partial agonists for the nicotinic acid receptor[117] aimed to treat atherosclerosis. It was postulated that partial agonism might result in tissue selectivity. The most potent member of the class, 5-butyl-pyrazole-3-carboxylic acid, **115**, had the greatest affinity for

the nicotinic acid receptor as measured by a competitive binding assay using rat spleen membranes. Recent patents claim similar 4,5-dialkyl-pyrazole-3-carboxylic acids,[118] as nicotinic acid receptor agonists.

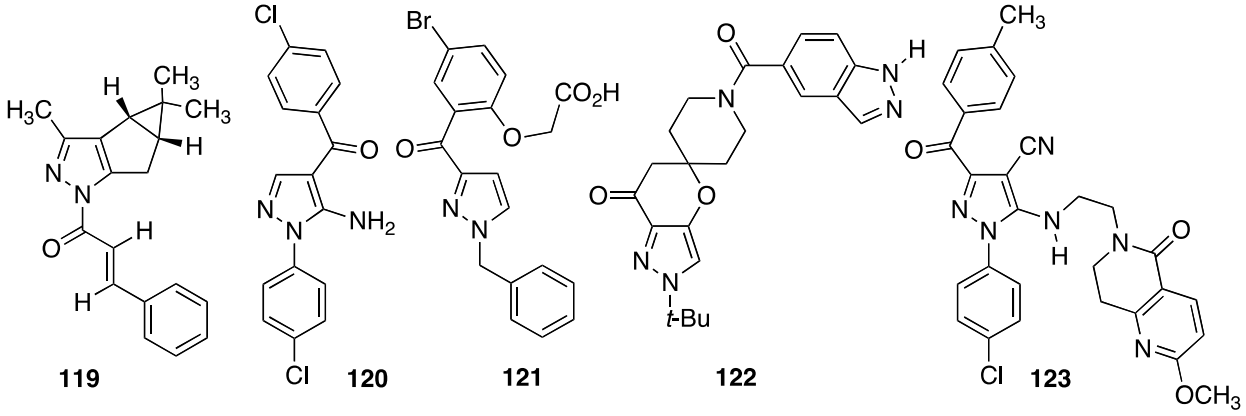
Pyrazole carboxylic acid **116** is a selective activator of the niacin receptor GPR109a, an interesting target for the treatment of atherosclerosis and dyslipidemia.[119]

Other pyrazoles with anti-lipidemic activity are compounds **117** and **118**.[117] It has been postulated that compared to full agonists, partial agonists may exhibit reduced adverse effects. Interestingly, compound **117**, a partial agonist in the GTPgS (guanosine 5'-O-[γ-thio]triphosphate) assay, turned out to be a full agonist in the cAMP whole-cell assay.[120] In addition, a series of 4-fluoro-5-alkyl pyrazole 3-carboxylic acids were also identified as selective agonists for GPR109a, a G-protein coupled receptor discovered in 1999 using data afforded by the Human Genome Project. As an extension of the cycloalkyl-fused pyrazole carboxylic acids, aryl substituents on the cycloalkyl group, particularly the cyclohexyl group, were also examined.[121] Compound **118** showed no significant flushing when administered to rats at the dose of 30 mg/kg.

7. Carbonyl compounds (Pz-CO-R)

7.1. *N*-substituted compounds

Pyrazole **119**, identified through HTS, is notable for its lack of a polar head group, and it served as the basis for the proposal of a pharmacophore model for S1P1 (sphingosine-1-phosphate receptor 1) agonism.[122] The S1P receptors are related to inflammation.



Scheme 12. Pyrazole carbonyl derivatives.

7.2. *C*-substituted compounds

The X-ray structure of compound **120**, a p38α inhibitor for treating metabolic diseases, shows a

hydrogen bonding interaction between the carbonyl oxygen of the benzophenone and Met-109 in p38α. In this case the carbonyl oxygen makes the crucial hydrogen bonding interaction with Met-109. The amino group at the 5 position of the pyrazole ring in compound **120** is involved in forming a hydrogen bond with Thr-106.[114,115] Compound **121** is a PGD_2 (Prostaglandin D_2) antagonist, developed for the treatment of allergic reactions, asthma, rhinitis, etc...[123] Pyranone **122** has interesting properties as an ACC1 and ACC2 (Acetyl-CoA-carboxylase) inhibitor and was studied for treating metabolic syndrome and diabetes.[124] Compound **123** which produces weight loss is a Ghrelin receptor inverse agonist.[125]

8. Amines

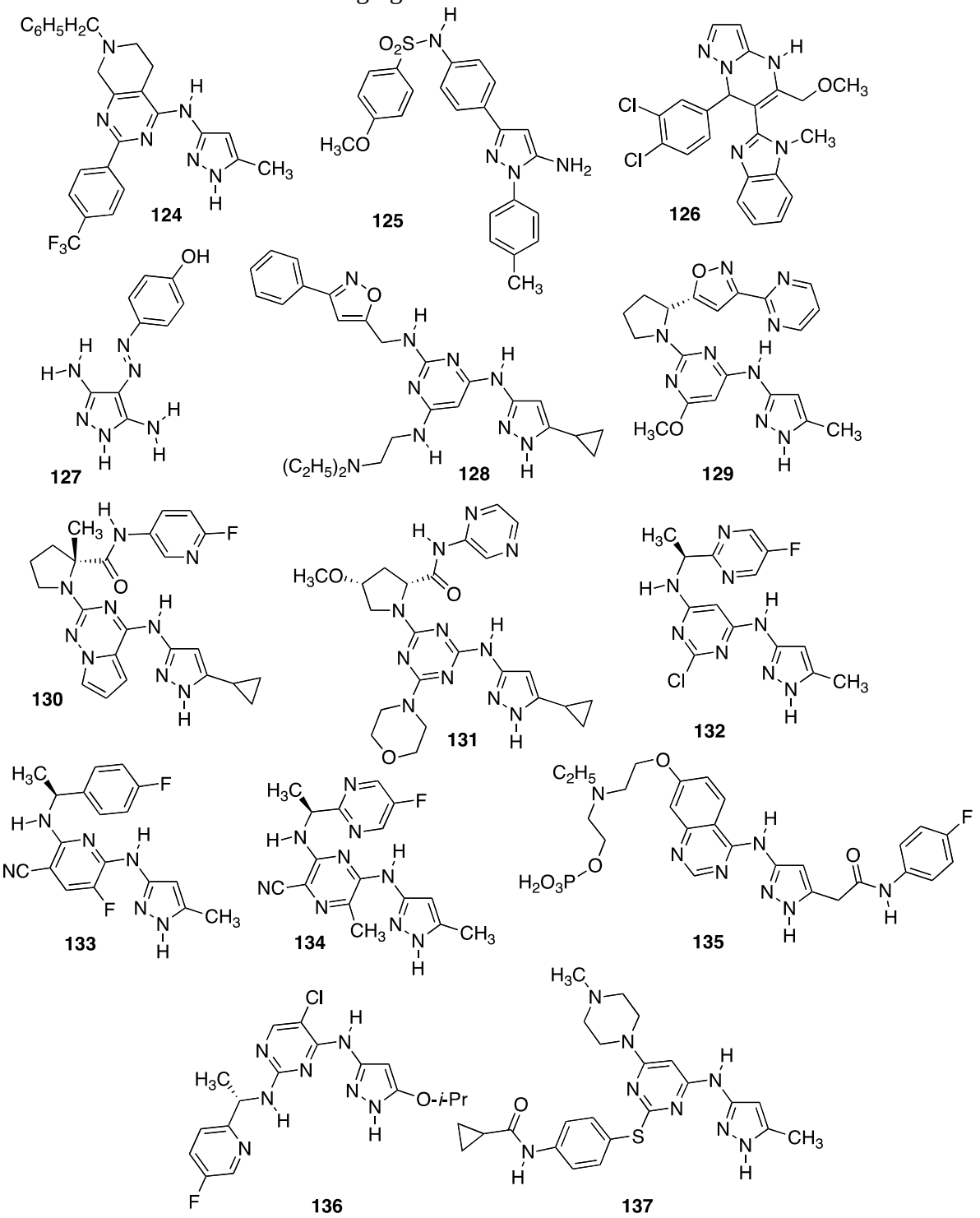
The molecules belonging to Section 8.1 are represented in Scheme 13.

8.1. Directly linked

Pyrimidine **124** claimed as a voltage-gated ion channel blocker useful for chronic and neuropathic pain has been described. Apart from screening assays, no other biological or selectivity data were presented, and therefore it is difficult to determine their potential as blockers.[126] In the obesity field, 5-aminopyrazole **125** is modestly potent (IC_{50} = 15 nM) but quite selective over the NPY_1 and NPY_2 receptors. Related pyrazoles with *N*-methyl substituents, either on the NH_2 or in the sulfonamide, provide derivatives with reduced affinity for the Y_5 receptor.[127] For the treatment of cardiac arrhythmia, the $K_V1.5$ channel antagonist **126** (the active enantiomer) showed long half-life and adequate bioavailability.[128]

One of the most prominent biological properties of aminopyrazoles is as anticancer drugs. 4-arylazo-3,5-diamino-1*H*-pyrazoles are CDK Inhibitors. A large family of these compounds was subject to SAR studies, selectivity, and cellular effects: the most interesting one was **127** whose crystal structure in complex with CDK2 was determined.[129] A number of inhibitors utilize the pyrimidine scaffold with various substitutions at the 2 and 4 positions. Pyrimidine **128** (XL-228) a representative of one of the series showed IGF-1R activity and advanced into the clinic. **128** is a potent Aurora kinase inhibitor that entered phase I study in patients with solid tumors or hematologic malignancies. A patent has been filed specifically claiming compound **129**, which has an IC_{50} of 4.3 nM with an eight-fold selectivity over the IR (insulin receptor). The aminopyrazole element is common to both **128** and **129** and most likely forms a hydrogen bond with the hinge region of the kinase.[130] Pyrrolotriazine BMS-754807, **130**, was reported as a 2 nM (IC_{50}) inhibitor of IGF-1R with no selectivity over IR and is orally active in a transgenically derived, Sal tumor model at a dose of 3 mg/kg.[131] The compound is also orally active at 3 mg/kg in the IGF-1R-driven sarcoma model and the Geo colon carcinoma model at 12 mg/kg. The combination of **130** plus Cetuximab (a monoclonal antibody) is therapeutically synergistic. Initial single ascending dose studies in normal healthy volunteers demonstrated good

bioavailability and tolerability. Further clinical evaluation was ongoing.[132] A similarly substituted triazine, **131**, is described in the patent literature which inhibits 96% of tumor growth in the I GF-Sal tumor model at a 3mg/kg oral dose.[132]



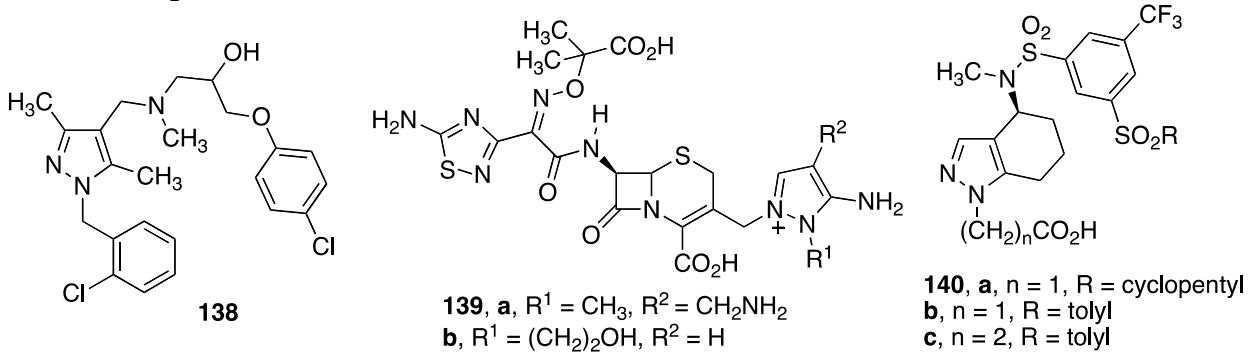
Scheme 13. Pyrazolylamines.

AZD1480 (**132**) is a pyrazolyl pyrimidine that reached Phase I clinical trials. The compound is a JAK1 and JAK2 ATP competitive inhibitor. AZD1480 is the first JAK2 inhibitor that suppressed growth of multiple solid tumors with constitutive STAT3 activation, thereby suggesting applicability beyond MPN indications for a JAK2 inhibitor.[133] AZ960 (**133**), a pyrazolo-nicotinonitrile analog, was reported to be a tight-binding, ATP-competitive JAK2 inhibitor. AZ960 also induced apoptosis in SET2 cells, which bear a constitutively active JAK2 pathway.[134] Modification of the **133** structure resulted in the identification of pyrazolylaminopyrazines, exemplified by compound **134**. In a mouse pharmacodynamic study, a single oral dose of **134** (25 mg/kg) demonstrated greater than 95% inhibition of STAT5 phosphorylation in splenic infiltrates of TEL (gene fusion)-JAK2 transfected Ba/F3 cells.[135] Compound **135** (AZD-1152) associates with 3 or 4 molecules of water, the stoichiometry depending upon relative humidity and temperature. However, a co-crystal with maleic acid, formed by combining the components in methanol, DMSO/methanol or DMSO at 60 ºC and precipitating by adding CH_3CN, is claimed to be both anhydrous and non-hygroscopic.[136]

Compound **136** (AZ-23), has been described with anticancer properties.[137] AZ-23 was a potent and selective Trk kinase inhibitor. In vitro studies with AZ-23 showed improved selectivity over previous compounds and inhibition of Trk kinase activity in cells at low nanomolar concentrations. AZ-23 represented a potent and selective Trk kinase inhibitor from a novel series with the potential for use as a treatment for cancer.[138]

The Aurore kinase inhibitor, VX-680 (**137**), inhibited TbAUK1 (*T. brucei* Aurore kinase) and disrupted cell cycle progression in the parasite *T. brucei* that causes African trypanosomiasis.[139]

8.2. With a spacer



Scheme 14. Aminomethylenepyrazoles.

N-Benzylpyrazole **138** (Scheme 14) inhibits LPS-induced nitric oxide production by binding to the MD2 (a 17 residue peptide) region that interacts with lipopolysaccharide-stimulated human whole blood. This kind of compounds may offer a new starting point for medicinal chemistry efforts to provide orally available TLR4 (Toll-like receptor 4) antagonists useful to treat CNS diseases.[140]

The excellent MIC results for FR26420 (**139a**), particularly against β-lactamase-producing strains was attributed to an extended SAR effort aimed at increasing the steric effect on the 3-position of the cephem nucleus culminating with the 4-position side chain on the pyrazolium ring. Key analogs (**139a** and **139b**) in the SAR regression illustrate the trend, with ceftazidime as a reference, in an experiment with an AmpC β-lactamase over-producing strain (FP 1380).[141]
A series of pyrazole acetic acids have been disclosed including **140a** and **140b** which possess CRTh2 (chemoattractant receptor homologous molecule expressed on Th2 cells; also known as DP2 or GPR44 or CD294) binding IC_{50} of 3 nM.[142] Interestingly, several propionic acid analogs, exemplified by **140c**, maintained high CRTh2 affinity (binding IC_{50} = 3 nM).

9. Alcohols and ethers

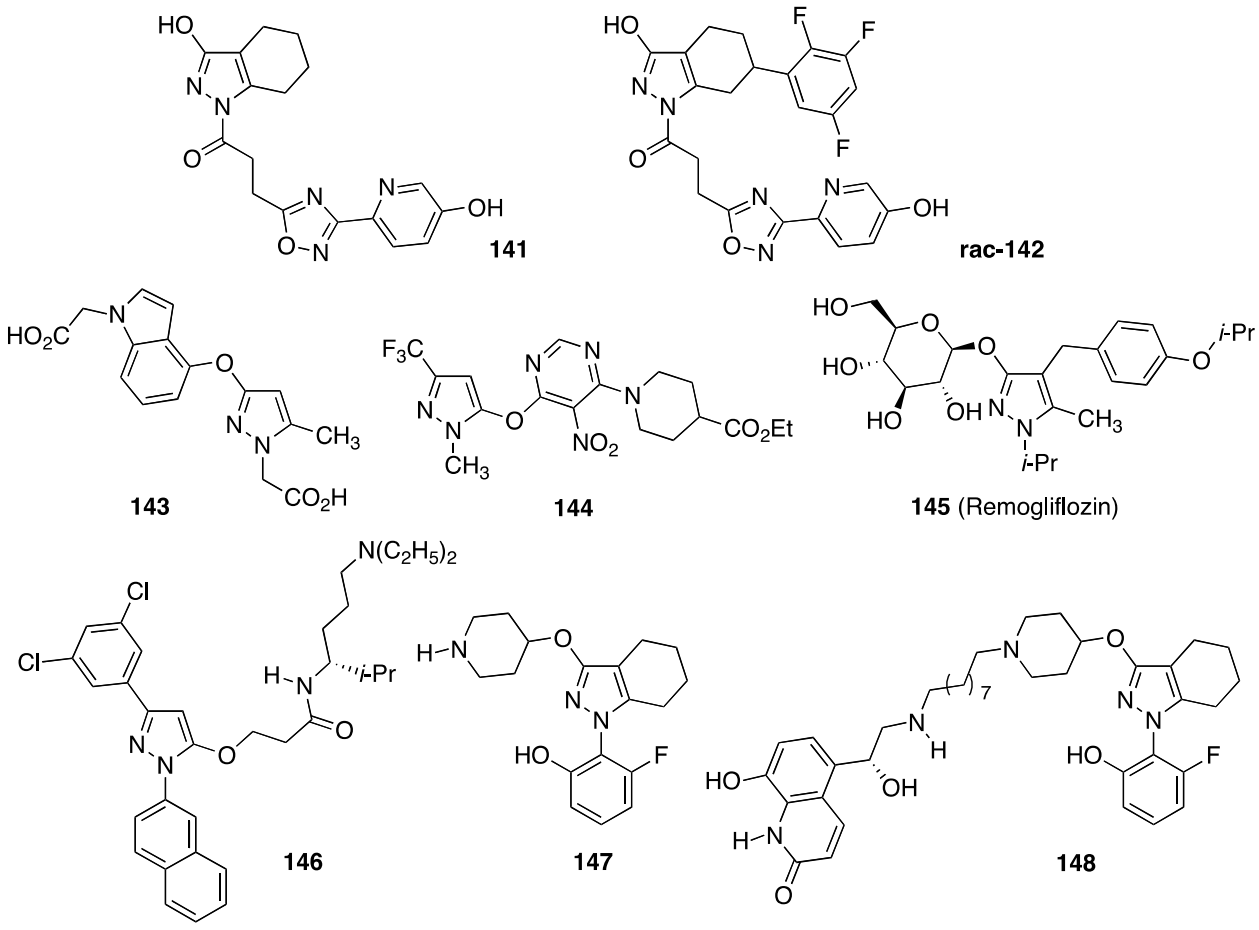
9.1. Directly linked

The main fields of application of compounds of this section are diabetes, inflammation and pulmonary diseases (Scheme 15).

Niacin (nicotinic acid) at high doses (>1 g/day) favorably modulates the human lipid profile by elevating high-density lipoprotein cholesterol (HDL-C) and decreasing low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), and lipoprotein a [Lp(a)]. Amongst other compounds, two 3-hydroxypyrazoles, **141** and **142**, showed affinity for the high-affinity niacin receptor GPR109a behaving as antagonists.[143]

In the field of Type 2 diabetes mellitus (T2DM), a patent disclosure detailed extensive efforts directed toward surrogates for the phenylacetic acid moiety of GW3965 (a non-steroidal liver X receptor agonist) as exemplified by pyrazole **143**.[144] Following a cyclase-based HTS campaign, pyrimidine **144** was identified as an inverse agonist of GPR119.[145] Optimization of **144** led to other GPR119 agonists.[146] In the field of T2DM, compound **145**, a glucoside-based SGLT2 (sodium glucose co-transporter 2) inhibitor, entered development but was discontinued due to lack of sufficient stability in the gut and post-absorption.[147]

In the field of inflammation, diaryl substituted pyrazoles have also been described as potent CCR2 antagonists. The diaryl pyrazole core was quite resistant to change. Compound **146** proved to be the most CCR2 active and also exhibited good selectivity over CCR5.[148]

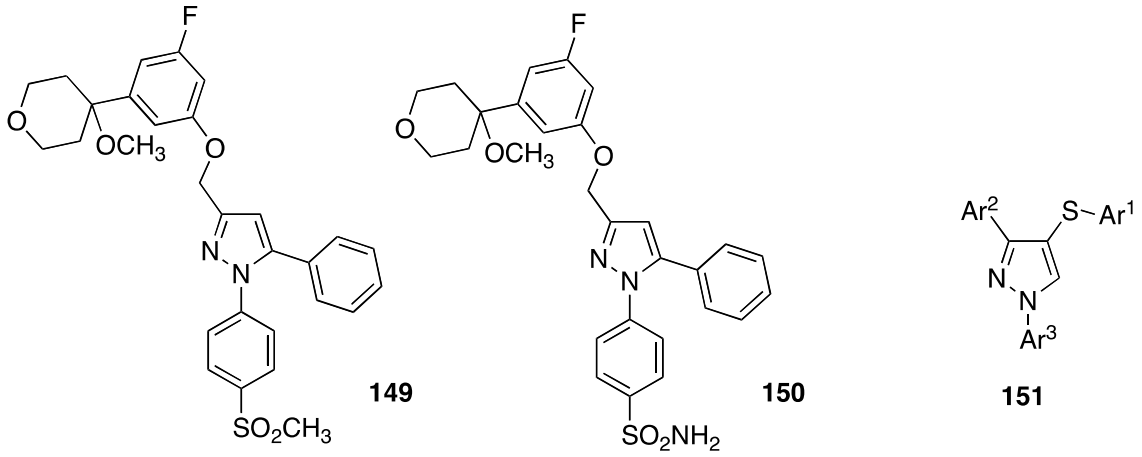


Scheme 15. Hydroxypyrazoles and their derivatives.

Related to pulmonary diseases such as COPD (Chronic obstructive pulmonary disease) are pyrazoles **147** and **148** that have unique muscarinic pharmacophores. One such example **146** began with a novel, selective M3 antagonist **147** which evolved from a nonselective norepinephrine reuptake inhibitor.[149] Compound **148** has high clearance in microsomes and poor membrane permeability, a favorable profile for an inhaled therapeutic.

9.2. With a spacer

In search for new compounds to treat inflammation, different classes of dual inhibitors have been described that combine the two key pharmacophores associated with known 5-LO (5-lipoxygenase) and COX inhibitors. Compounds **149** and **150** exemplify one of these classes, dual inhibitors that combine the pyrazole triaryl motif of the selective COX-2 inhibitor Celecoxib (**218**) with the tetrahydropyranylphenyl pharmacophore found in the non-redox 5-LO inhibitor ZD-2138. They displayed balanced 5-LO/COX-2 inhibition and are as efficacious as Zileuton and Rofecoxib in a rat model of AA-induced ear edema.[150,151]



Scheme 16. Derivatives of hydroxymethylenepyrazoles

9.3. With a N-O bond

N-Hydroxypyrazoles and pyrazole *N*-oxides are not very common compounds, but compound **84** is included in Section 4.2.

10. Thiols and thioethers

A series of compounds of general formula **151** (Scheme 16) are non-covalent FAAH (fatty acid amide hydrolase) inhibitors and therefore potentially useful for pain treatment. In no case has the *in vivo* analgesic efficacy been reported for these compounds. However, assuming these compounds are indeed active *in vivo*, they would provide an alternative approach to irreversible covalent inhibitors that might eliminate potential safety concerns over the creation of long-lived covalent adducts between compounds and the FAAH enzyme.[152]

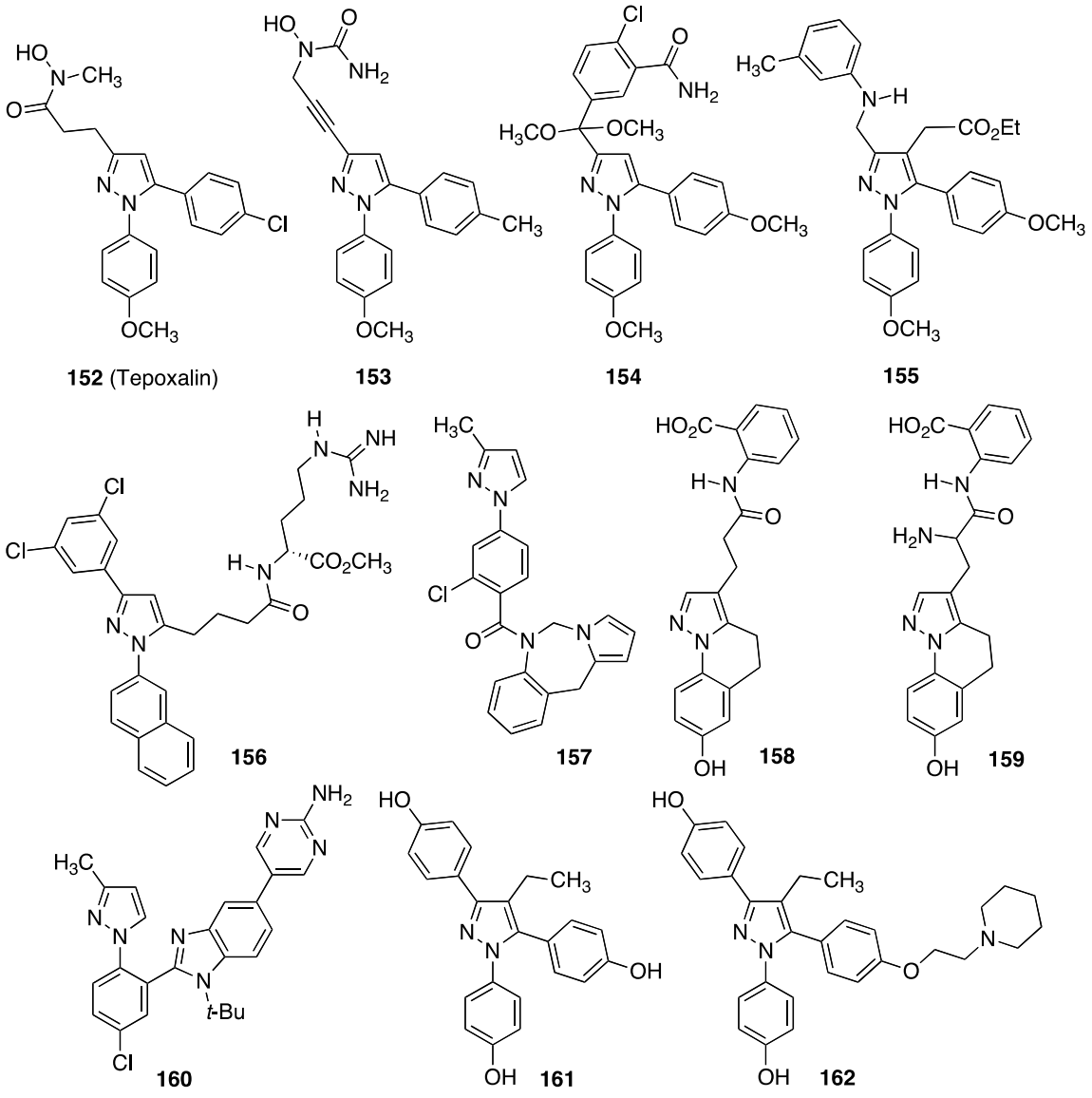
11. Aromatic substituents

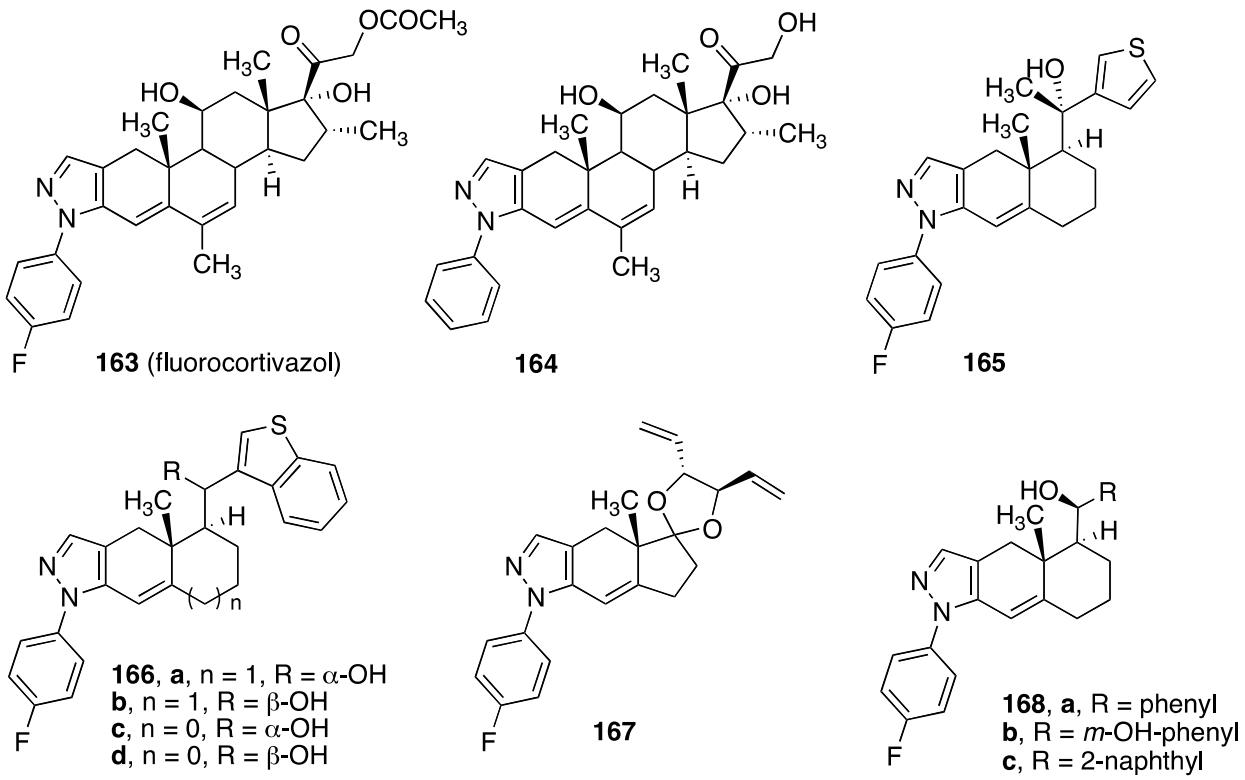
11.1. *N*-substituted compounds

11.1.1. Directly linked. One of the *N*-aryl derivatives summarized in Scheme 17 is the pyrazole-containing hydroxamic acid **152**, also known as Tepoxalin, a non-steroidal anti-inflammatory drug with a dual action 5-LO/COX.[153] It is prescribed for treatment of pain and inflammation associated with canine osteoarthritis. Structurally related to the redox 5-LO inhibitor ABT-761 bearing an acetylenic *N*-hydroxy urea group is compound **153**. In a canine blood *ex vivo* assay this dual inhibitor displayed a short-lived inhibition of COX and 5-LO.[154]

Compounds **154** (ER-34122) and **155** are examples of pyrazoles with three aryls based on Celecoxib and Tepoxalin structures exhibiting a dual inhibition profile.[155,156] Moreover, **154** resulted to be 3- to 10-fold less potent than Indomethacin in inhibiting carrageenan-induced rat paw edema. Diaryl substituted pyrazoles have also been described as potent CCR2 antagonists. Compound **156** showed CCR2 (IC_{50} =221 nM) and CCR5 (IC_{50} =63 nM) activity.[148]

The V2 receptor is mainly localized in the kidney and is responsible for fluid homeostasis. Compound **157** reached phase II clinical trials for enuresia.[157] A potent generation of GPR109a agonists was discovered after hybridization of bicyclic and biaryl anthranilides. One of these compounds, **158**, showed good activity against GPR109a, a good mouse PK profile, a superior TI over niacin regarding FFA reduction and vasodilation effects in rats, and minimal CYP2C8 (Cytochrome P_{450} 2C8) and CYP2C9 (Cytochrome P_{450} 2C9) inhibition liability.[158]





Scheme 17. *N*-arylpyrazoles.

A strategy to obtain new compounds was achieved replacing the phenyl group of anthranilic acid by a cycloalkene. Additionally, substitution of the central ethylene linker by an amino group was reported being **159** an example. This may have beneficial effects such as better physical properties and a reduced IC_{50}.[159] LT signaling is known to be involved in processes associated with atherosclerosis. Several patent applications related to FLAP inhibitors of different scaffolds such as benzimidazoles (e.g. **160**) have been reported.[160]

The unique tissue selectivity found in selective estrogen receptor modulators (SERMs) has proven beneficial for the treatment of diseases such as breast cancer and osteoporosis. They mimic estrogen (E2) in some tissues, such as bone, while suppressing its effects in other tissues, such as the breast and uterus. The transformation of ERa agonists into modulators has been achieved by appending a basic side chain at the appropriate position. An example can be found in the transformation of the pyrazole agonist **161**. Attaching a piperidinylethyl side chain it is transformed into compound **162**, a full antagonist on ERa (IC_{50} ~20 nM) and is ~18-fold selective for ERa.[161]

Compounds **163** and **164** were reported as glucocorticoid receptor (GR) agonist analogs of Fluorocortivazol.[162] Modifications of the C- and D-rings of **164** led to compound **165** (IC_{50} = 0.8 nM) without losing activity. This potent GR ligand showed activity in both TR (interleukin 6 (IL-6) inhibition in human A549 lung carcinoma cells (EC_{50} = 1.0 nM, 97% efficacy) and TA (tyrosine amino transferase (TAT) induction in human HepG2 cells (EC_{50} = 36 nM, 69%

efficacy) functional assays. In a lipopolysaccharide-stimulated mouse model of tumor necrosis factor-alpha production (LPS-TNFa) **165** showed an ED_{50} of 4 mg/kg (p.o.).[163]

Conversion of the thiophene ring to benzothiophene and removal of the tertiary methyl group (**166a**) did not affect GR binding affinity (IC_{50} = 1.5 nM) or dissociative activity in TR and TA assays.[164] Changing to the other hydroxyl epimer (**166b**) does not influence GR binding, although it confers dissociation when examined in TR (IL-6 inhibition EC_{50} = 18 nM, 86% efficacy) and TA (TAT efficacy 21%) assays. Contracting the B-ring of **166a** and **166b** from a 6- to a 5-membered ring (**166c** and **166d**) affected the biological and pharmacokinetic (PK) properties.[165]

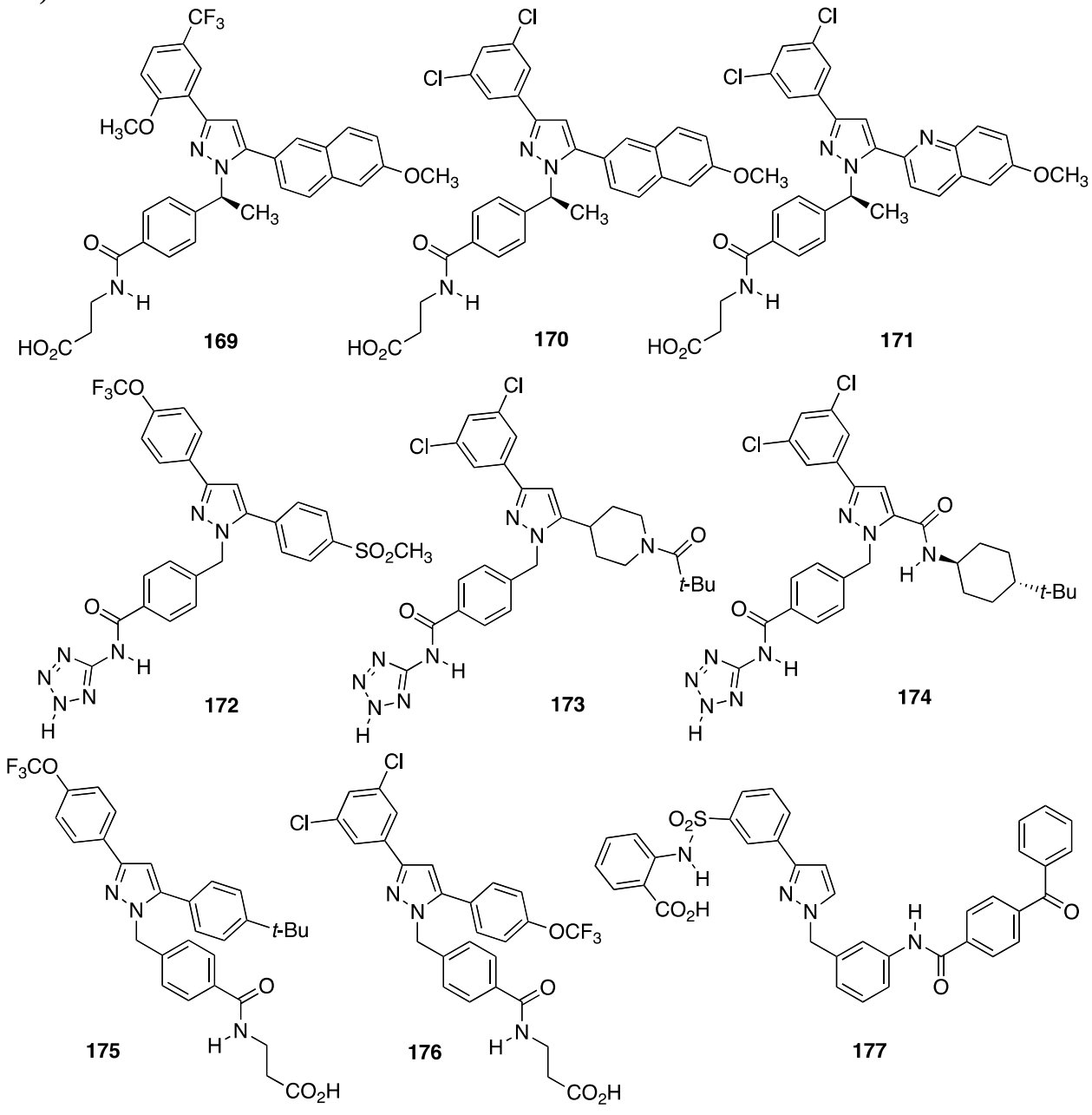
Compound **166c** showed its effectiveness in the TR assay (IL-6 inhibition EC_{50} = 10 nM, 92% efficacy) but resulted less efficacious in the TA assay (TAT induction EC_{50} = 675 nM, 62% efficacy). Besides, **166c** improved the PK profile and notably reduced *in vivo* TNFa production. In contrast, **166d**, the hydroxyl epimer of **166c**, was less effective in TR and TA assays (IL-6 inhibition EC_{50} = 5 nM, 71% efficacy; TAT efficacy 29%).

Replacing the conventional C- and D-rings of steroidal glucocorticoids with a variety of substituted ketals differing in ring size resulted in a novel series of potent and selective nonsteroidal ligands with a comparable GR binding potency and steroid receptor selectivity in vitro to that of marketed glucocorticosteroids.[166] For instance, **167** is a potent and selective GR ligand (GR IC_{50} = 8 nM) with a partial agonism profile in TR and TA assays (IL-6 inhibition EC_{50} = 2.6 nM, 58% efficacy; TAT efficacy 11%). Its good murine PK profile led to an effective TNFa inhibition *in vivo* (ED_{50} = 14 mg/kg, p.o.).

Other C- and D-ring modified Fluorocortivazol analogs such as **168a** and **168b** were tested for TA and TR in osteosarcoma cells.[167] They showed equal affinity for GR (IC_{50} = 5-8 nM) and full agonism activities in TR assays (nuclear factor kB (NFkB) EC_{50} = 3 nM, 63-68% efficacy; activating protein 1 (AP-1) EC_{50} = 3 nM, 73–112% efficacy) and a TA assay (mouse mammary tumor virus, MMTV) EC_{50} = 3 nM, 99–133% efficacy). Nevertheless, analog **168c** (GR IC_{50} = 2 nM) resulted to be more potent in the AP-1 assay (EC_{50} = 3 nM, 71% efficacy) than the NFkB (EC_{50} = 74 nM, 54% efficacy) and the MMTV assays (EC_{50} = 22 nM, 127% efficacy). Their ability to affect 17 GR target genes was studied using quantitative real-time PCR in A549 human lung adenocarcinoma cells.[168] This study showed that subtle differences in the shape of the ligands has a great influence on the transcriptional regulatory activities of GR, and the endogenous genes bearing natural GREs.

11.1.2. With a spacer. Treatments based on glucagon receptor antagonists are expected to improve the glycemic control in T2DM patients. Several pyrazole-based analogs have appeared in the patent literature.[169] Their main structural characteristics can be summarized as follows: three substituents around the pyrazole nucleus one of which is a β-alanine or aminotetrazole-derived benzoyl group. Attention has been focused on pyrazoles **169** and **170** in which the pyrazole ring is substituted by an aryl and a fused bicyclic aryl ring system. Phenyl pyrazoles bearing an alkoxy- and trifuoromethyl-phenyl substitution like **169** exhibited a potent binding

and functional activity towards human glucagon receptor (hGCGR cAMP IC_{50} = 5–50 nM). Besides, chloro-substituted derivatives such as **170** displayed moderate to high binding affinities (hGCGR IC_{50} = 1–500 nM). Pyrazole derivative **171** substituted with a bicyclic heteroaryl group has also been included in a patent application as well as the diphenyl-substituted pyrazole exemplified by **172** and cycloheteroalkyl-substituted pyrazoles such as **173**. Finally, pyrazole carboxamides such as **174** were disclosed with moderate to high binding affinity (IC_{50} = 1-500 nM).



Scheme 18. *N*-benzylpyrazoles.

A novel series 1,3,5-pyrazoles of glucagon receptor antagonists were published in 2011 with improved PK and PD properties; amongst them, compound **175** had hGCGR IC_{50} values of 480 nM and **176** had an IC_{50} = 95 nM.[170]

Compound **177** was reported as a Dengue virus inhibitor. Pyrazole derivative **177** irreversibly inhibited NS5pol (IC_{50} = 1.5 μM). Based on a structural analysis of the available X-ray structure and docking experiments, a binding mode was proposed at a site between the "finger" and "thumb" regions of the polymerase.[171]

11.2. *C*-substituted

Scheme 19 compiles C-arylpyrazoles with a great variety of applications, from analgesia to metabolic syndrome, cancer and HCV. Non-selective sodium channel blockers are used as analgesics. Na_v channels are formed by a pore forming alpha subunit and an auxiliary beta subunit. In 2010, a patent application disclosed a series of potent $Na_v1.7$ blockers.[172] Estimated IC_{50} values for $Na_v1.7$ using a PatchXpress platform were reported in the single nanomolar to picomolar range for a number of examples. One of the compounds prepared in multigram quantities was compound **178**.

A way to develop small molecules to disrupt protein-protein interactions is a strategy known as fragment assembly. Fragments with affinity for the target are connected to yield more potent molecules. Based on lead compound **179** and following this methodology, a potent small inhibitor **180** (IC_{50} = 60nM) of the IL-2 I IL-2Ra was found.[173]

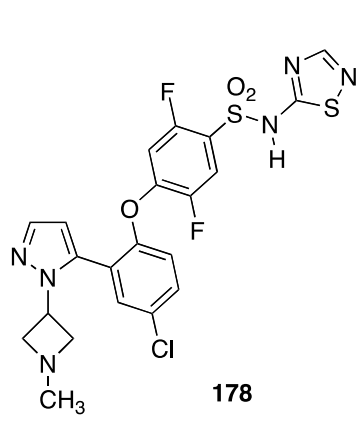
Cat S, found predominantly on antigen presenting cells, has been considered a therapeutic target for asthma. Progress towards Cat S selective inhibitors has been reported such as pyrazole-based inhibitor JNJ-10329670 (**181**) with a Cat S potency (IC_{50} = 100 nM) and selectivity over other cathepsins including Cats K and L (IC_{50} >50 μM).[174] The azaindole **182** showed an improvement as Cat S inhibitor (IC_{50} = 30 nM) and in the cellular tests (IC_{50} = 38 nM).[175]

For the treatment of type 2 diabetes and metabolic syndrome the pharmacological inhibition of 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1) activity has been proposed as a therapeutic strategy. Triazoles belong to a class of 11 β -HSD1 inhibitors and have been covered in the patent literature. Besides, pyrazole derivatives have also shown 11β-HSD1 potency. For instance, compound **183** had a reported IC_{50} value of < 10nM.[176]

Dual inhibitors of ACC1 and ACC2 based on a conserved spirochromanone core have been reported. A more recent patent expanded the scope of the structures (e.g. **184**, 100% inhibition of human ACC1 and ACC2 at 1 μM).[177] It was also found that a number of five-membered heterocyclic rings could be located at the 6 position of the spirochromanone ring such as pyrazole **185** (rat ACC1 IC_{50} = 7.4 nM, LE = 0.34). The pyrazole derivative **186** was reported as a non-*N*-hydroxyurea selective non-redox 5-LO inhibitor showing an IC_{50} of 130 nM in a human whole blood assay.

Cystic fibrosis (CF) is a lethal genetic illness caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR), an epithelial chloride-and bicarbonate-

selective ion channel activated by cyclic AMP-dependent protein kinase A. HTS identified the CFTR enhancer **187** exhibiting a measured EC_{50} of 2.4 μM.[178]



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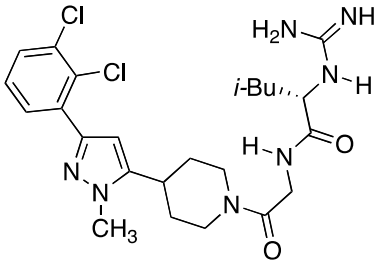

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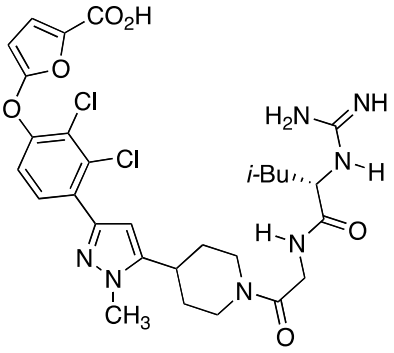

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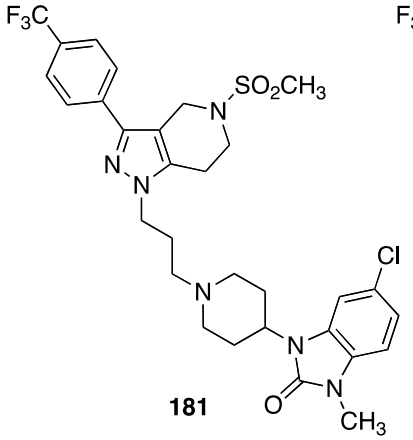

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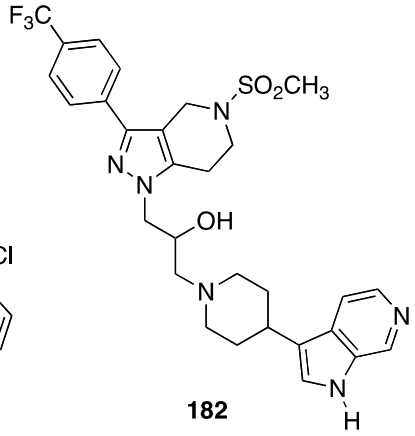

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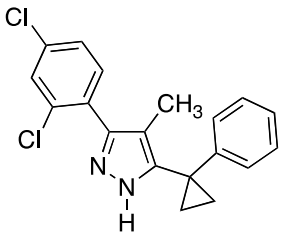

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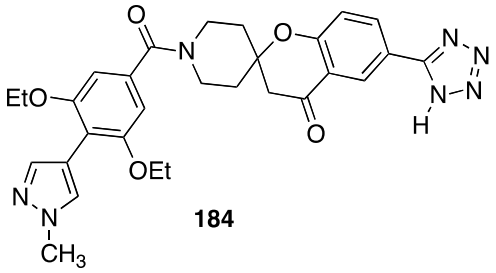

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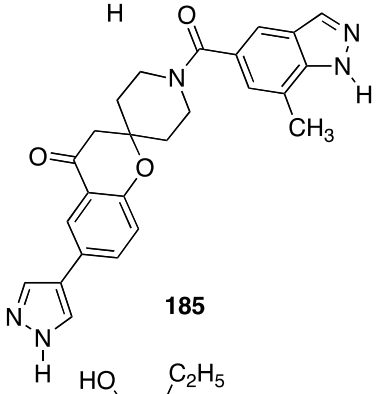

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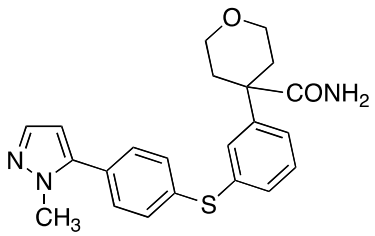

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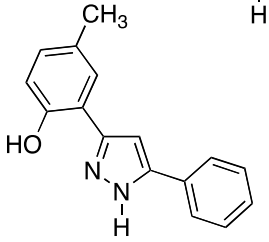

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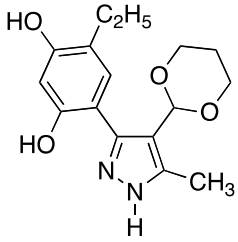
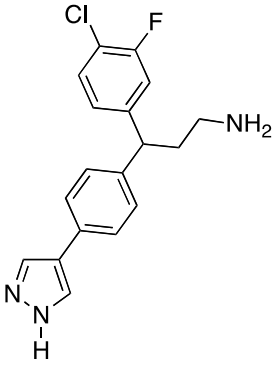


188 (CCT 018159)



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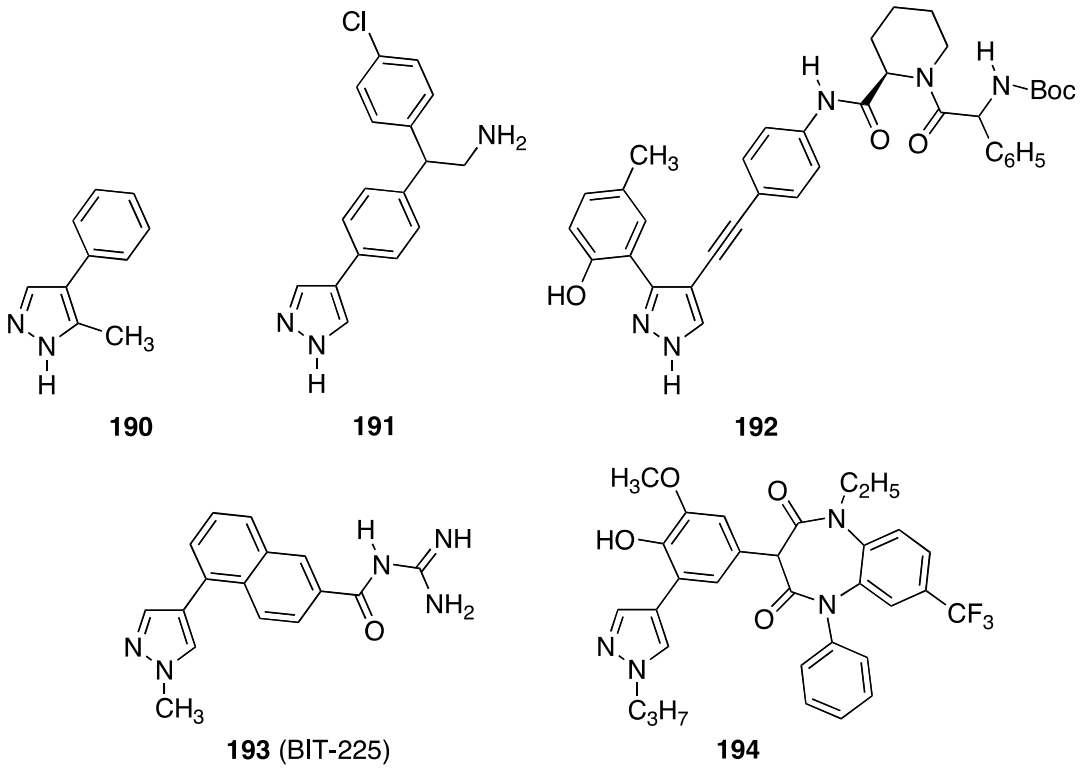


Scheme 19. *C*-Arylpyrazoles.

Small molecular scaffolds have been pursued in order to circumvent the disadvantages associated to natural products inhibitors of Hsp90. As an example, pyrazole CCT018159 (**188**) was reported.[179] It maintained the critical binding resorcinol moiety of radicicol, inhibited the ATPase activity of Hsp90 with a low micromolar IC_{50} as well as the proliferation of several tumor cell lines at similar concentrations (~ 8 μM).

PI3K/Akt pathway is considered a potential target for cancer therapy. A series of pyrazoles were disclosed in a patent application as AKT inhibitors,[180] pyrazole **189** showing an AKT activity of IC_{50} < 0.1 μM.

Another target for cancer therapy closely related to the PI3K/Akt pathway is the PKB (Akt). PKB is involved in the PI3 kinase-PKB-mTOR cellular signaling pathway. Fragment screening (bioassay or X-ray) led to different PKB binding fragments (e. g. **190**). From hit **190** and using a fragment growing approach, the lead **191** was obtained and it bound to the ATP pocket.[181]

Compound **192** has been reported as a HCVNS5 inhibitor with an EC_{50} ~ 1 μM. It was included in a patent application of HCVNS5 inhibitors based on homoproline and its isosteres.[182]

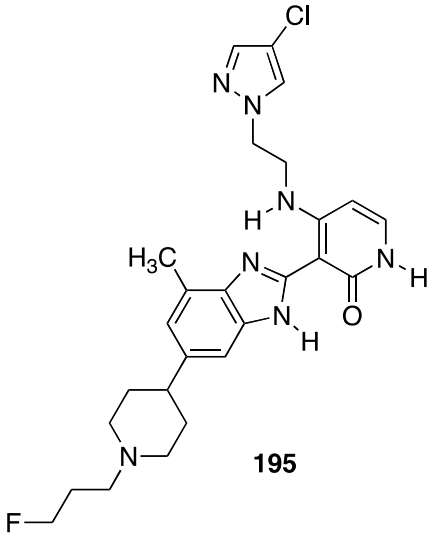
Another pyrazole derivative described with antiviral properties is compound **193**. It is related to the pestivirus bovine viral diarrhea virus (BVDV), EC_{50} = 314 nM, and HIV-1 in cell culture, EC_{50} = 2.25 μM consistent with inhibition of Vpu which is involved in virus assembly.[183,184]

Even though the capsid assembly (CA) is common to viral replication and infectivity, it has not been the subject of extensive drug discovery programs until a couple of years ago. Two

chemical series were identified through NMR spectroscopy as binding to CA_{NTD} and inhibiting HIV-1 replication.[185] A representative of one of the series is compound **194**, a benzodiazepine derivative which exhibited an EC_{50} = 70 nM and low toxicity for a 50% reduction of cell proliferation against uninfected cells (CC_{50}) of 28 μM.

12. Aliphatic substituents

This section is rather artificial. We have placed here compound **195** that has none of the substituents of the previous or subsequent sections. In the field of small molecule inhibitors of IGF-1R, pyrazole **195** (BMS-695735) was discovered showing *in vivo* efficacy against colon carcinoma and myeloma.[186] GSK 625433 (**196**) was reported as a very promising drug for the treatment of hepatitis C by inhibiting the HCV NS5B polymerase.[187,188]



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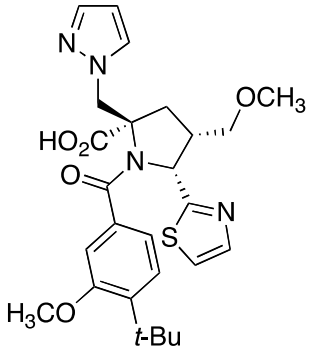


196 (GSK 625433)

Scheme 20. *C*-alkylpyrazoles

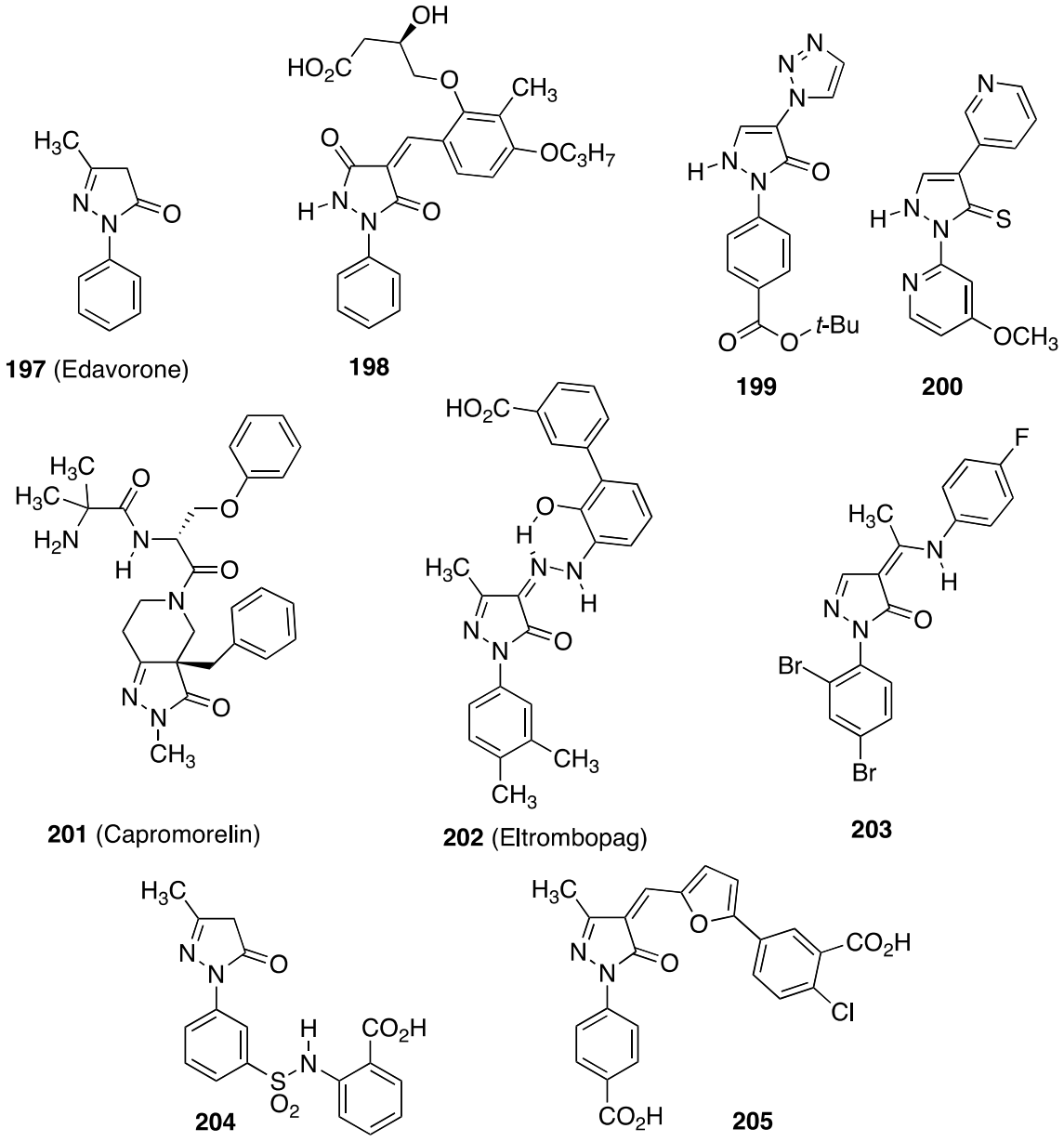
13. Non aromatic compounds

13.1. Pyrazolones

3-Hydroxypyrazoles, although having a pyrazolin-3-one tautomer, exist as 3-hydroxy tautomers and therefore have been discussed in section 9.1.

Edavorone (**197**) was introduced in the market by Mitsubishi Pharma in 2001 as a neuroprotective agent (improving neurological recovery following acute brain infarction).[189] Pyrazolin-3,5-dione, **198**, an antithrombotic agent, acts as an antagonist of the platelet $P2Y_{12}$

receptor.[190] Inhibitors of HIF prolyl hydrolases are useful for the treatment of anemia, amongst them structures **199** (a pyrazolin-5-one) and **200** (a pyrazolin-5-thione).[10] Capromorelin, CP-424,391 (**201**), a tautomerism blocked pyrazolin-5-one, proved to increase body weight in rats after extended treatment without concomitant changes in body fat or lean mass.[191-194] It was considered as a Ghrelin mimetic.



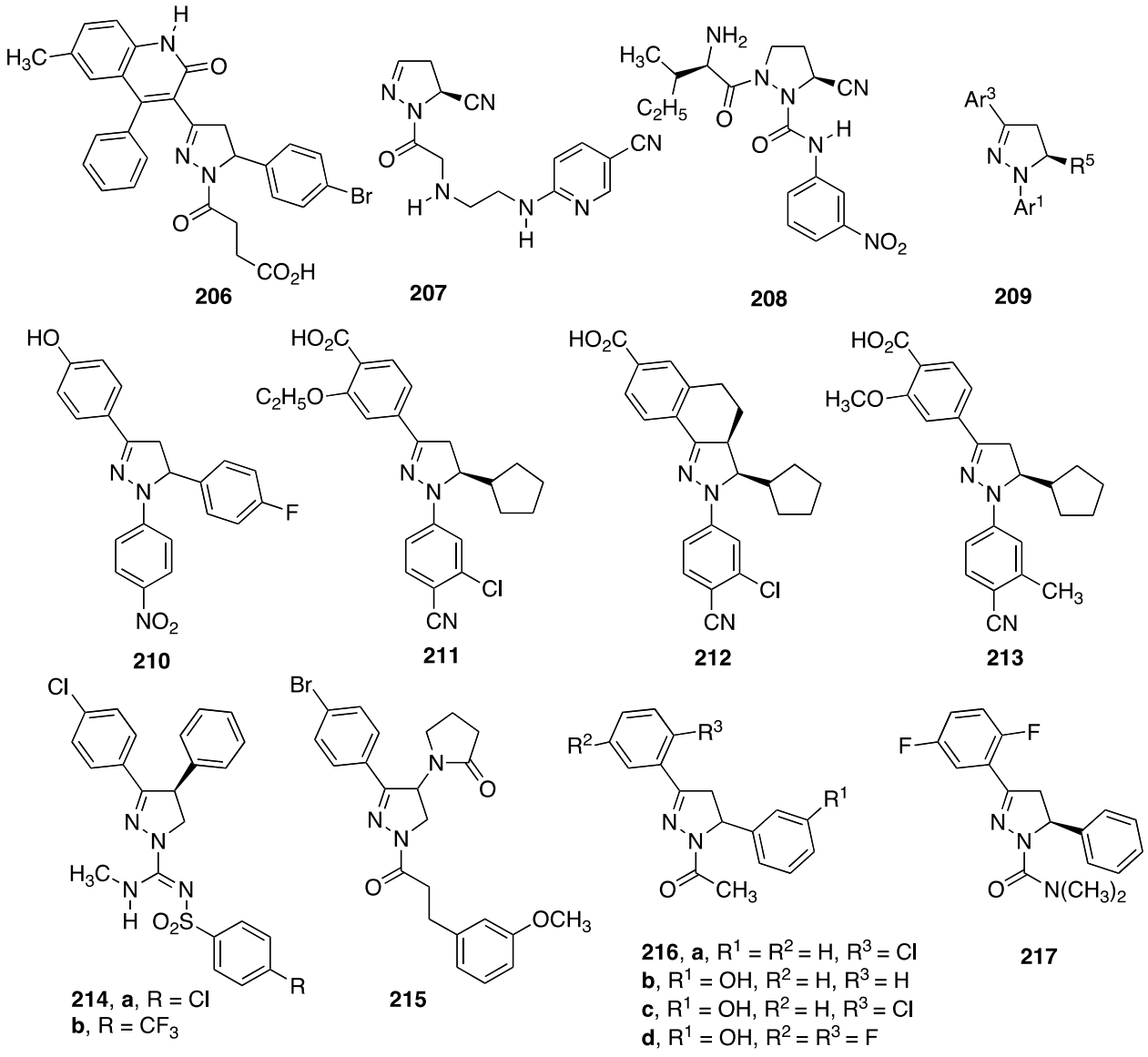
Scheme 21. Pyrazolones and related compounds.

GlaxoSmithKline introduced Eltrombopag (**202**) in 2008 as an antithrombocytopenic agent to treat ITP (idiopathic thrombocytopenic purpura), an autoimmune disease.[195] The monastrol (a

dihydrothiopyrimidine) enhancer **203** was discovered searching for novel anti-cancer agents.[196] A HTS of more than 1 million compounds against the full-length NS5 protein resulted in the discovery of **204** a lead for the treatment of dengue viral illness.[197] MUT11931 **205** was a lead compound in a series of inhibitors of WaaC (a glycosyltransferase essential for inner core lipopolysaccharide biosynthesis) developed to eliminate antibiotic resistance.[198]

13.2. Pyrazolines

In this section there are several *N*-acyl derivatives (**206**, **207**, **208**, **215**, **216** and **217**) that can be considered examples of Section 7.a. The fact that *N*-acylpyrazoles (only example **119**) are rare while *N*-acylpyrazolines are common is related to the properties of azolides.[199,200]



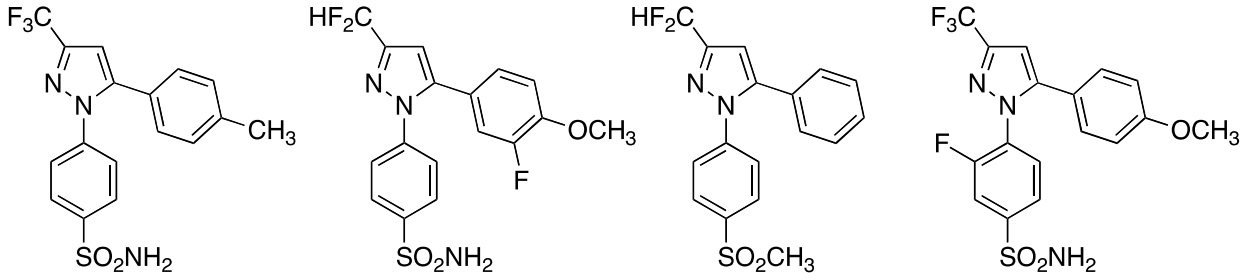
Scheme 22. Pyrazolines (4,5-dihydropyrazoles) and related compounds.

Pyrazoline **206** bearing a quinolone substituent at position 3 acts on the glutamate receptors (GluN2C and GluN2D) and has potential for the treatment of Parkinson's disease.[201] 5-Cyano-2-pyrazoline **207**[202] and 5-cyanopyrazolidine **208**[203] were described as inhibitors of dipeptidyl peptidase 4 (DPP4) an ubiquitous serine protease that modulates the biological activity of glucagon-like peptide-1 (GLP-1). GLP-1 plays an important role in the control of glucose levels. GLP-1 has shown efficacy in diabetes, but suffers from a very short physiological half-life due to DPP4-mediated cleavage of the active peptide to an inactive form. A series of pyrazolines of general formula **209** (R^5 = 5-fluorophenyl or cyclopentyl, structures **210** to **213**) possessing MR antagonist activity were developed for the treatment of hypertension.[204,205] Compound **212** (PF-3882845) was shown to decrease urinary albumin, reduce blood pressure and protect against kidney damage in rats. For these reasons it was chosen to advance in clinical studies for diabetic nephropathy.

Structurally distinct from the pyrazoles of section 4.c. is a series of 3,4-diarylpyrazolines. Based on *in vitro* and *in vivo* pharmacological data, (SLV-319 **214**) as well as its close analog (SLV326 **215**) were characterized as potent CB1 antagonists which displayed *in vivo* activity similar to rimonabant (**104**) in several pharmacological models.[206,207] In the field of anticoagulant-antithrombotic agents, pyrazoline antagonists of PAR-1 (protease activated receptor), exemplified by pyrazoline **215** have been reported.[208]

Several pyrazolines have been published as anti-cancer agents.[209-213] Compounds **216** and particularly **216d** were identified as screening hits with ATPase IC_{50} values of 3.6 and 6.9 mM, respectively. Exploration of N1-substitution with larger acyl or alkyl groups generally resulted in analogs with lower potency, whereas compound **217** with a dimethyl urea had similar potency to compound **216d**.[210]

14. Fluoro derivatives (F, CF_3)



218 (Celecoxib) **219** **220** **221**

Scheme 23. Pyrazoles bearing CF_3 or CF_2H substituents.

Celebrex (Celecoxib) **218** is a pain drug known as a COX-2 selective non-steroidal anti-inflammatory drug (NSAID) or a COX-2 inhibitor. Celebrex was widely prescribed to relieve arthritis and menstrual pain. Although Celebrex has been linked to an increased risk of heart

attack and stroke, the risk associated with it is similar to the risk associated with the other non-selective NSAIDs, except aspirin. The number of references related to Celecoxib is very large; the interested reader can consult those reported in the *ARMC*.[214-217] For a recent review, see ref.[218]

Another COX-2 inhibitor is Deracoxib (**219**), trade name Deramaxx (Novartis), used in veterinary medicine to treat osteoarthritis in dogs, in particular for the control of post operative pain and inflammation associated with orthopedic surgery.[219] Selectivity COX-2/COX-1 has been considerably increased in pyrazole **220**.[220] Compound **221** had similar potency and selectivity to Celecoxib in enzyme assays.[221]

In the course of this review several compounds bearing CF_3 substituents have been mentioned: **1**, **4**, **49**, **50**, **52**, **58**, **62**, **63**, **66**, **68**, **70**, **71**, **72**, **73** and **74**. These structures belong to Sections 3 (Heterocycles) and 4 (Amides). This observation is certainly significant, either CF_3 groups in other sections have not led to interesting compounds, or it will be interesting to explore the effect of the CF_3 (or CF_2H) substituents in the structures reported in Sections 5 to 13. On the other hand, directly fluorinated pyrazoles (C-fluoropyrazoles) have only one representative, compound **116**. This is not because F is a less interesting substituent than CF_3 but on account of the greater practical difficulty of making C-F pyrazoles,[222-225] compared with the ease with which C-CF_3 pyrazoles can be prepared.[226-240]

15. Conclusions

When reading publications or attending lectures one is always surprised by the introductions where always the compounds under study have important applications, mainly in medicinal chemistry, to the point that it has been written that the most important pharmacophore is the phenyl ring because it is the most common feature in drugs.[241] In the field of azoles, some of them are constituents of natural biomolecules: pyrrole (porphyrins, heme, chlorophyll, etc.), indole (tryptophan, serotonin, etc.), imidazole (histidine, histamine, etc.) and benzimidazole (vitamin B_{12}); the remaining ones are xenobiotic. 1*H*-Tetrazoles have been used as carboxylic acid isosteres, 1,2,3-triazoles are less common but with the discovery of the click reactions their importance will increase. Pyrazoles and 1,2,4-triazoles are probably the most frequently found heterocyclic rings in medicinal chemistry although indazoles are becoming important.

The large number of pyrazoles [243 (taking into account that several include more than one structure) for the 2002-2012 period] reported in this review is but the tip of the iceberg. A conservative estimate is that the number of studied pyrazoles is 10 or 100 times larger, in the order of thousands.

When discussing toxicity it must be taken into account that this fact does not have the same relevance in the treatment of cancer as, for instance, in the treatment of high-blood pressure; or for a disease where several safe drugs already exist than, say, for an orphan drug (a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the

condition itself being referred to as a rare disease). However, that a very relevant drug with a pyrazole skeleton, Rimonabant (**104**) had to be withdrawn because of its psychiatric problems (depression) is not a good result concerning the safety of pyrazole derivatives. On the other hand, although Celebrex (Celecoxib) (**218**) has been associated with cardiovascular thrombotic (stroke) and gastrointestinal (perforation) events it continues to be a reference compound in the field of anti-inflammatory painkillers.

We hope that the present review will promote the use of the pyrazole scaffold and will show the type of structures that have been explored and, by exclusion, how many have not been used to explore their biological activities. Besides, some patterns appear relating the structure and the pharmacological field, this also should be considered when designing new pyrazoles in medicinal chemistry.

Acknowledgements

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