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THE PYRAZOLE SCAFFOLD IN DRUG DEVELOPMENT. A TARGET PROFILE ANALYSIS

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ABSTRACT: The study investigates the pyrazole ring as a scaffold in drug development, focusing on identifying its privileged biological targets. Molecular descriptors distributions were used for characterizing the pharmacologically active pyrazole derivatives in order to provide rule of thumb for design of new drug like pyrazoles. The analysis of the biological interaction profiles demonstrated a class-selectivity of these compounds toward protein kinases involved in cancer pathology, highlighting the importance of the pyrazole moiety in the development of new antitumor drugs. Several other targets with implications in different pathologies were revealed. Our study indicates the pyrazole ring as an attractive framework for drug discovery, pyrazole-based derivatives being capable of serving as ligands for a diverse array of molecular substrates, depending on the varying substituents.
Keywords: privileged scaffolds, target affinity patterns, database mining, adenosine bioisoster, virtual screening

INTRODUCTION:

The pyrazole moiety is scarcely found in nature. Only a few natural compounds with a pyrazole-based structure were isolated. 1*H*-pyrazole-3-carboxylic acid and 4-methylpyrazole-3(5)-carboxylic acid were identified in the methanol extract of *Tedania anhelans* (Parameswaran *et al.,* 1997). *β*-Pyrazol-1-yl-alanine is an amino acid isolated from water-melon seeds (Lachlan *et al.,* 2013). Formycin and pyrazofurin are pyrazole derivatives with antibiotic activity isolated from *Nocardia interforma* and *Streptomyces candidus*, respectively (Henderson *et al.,* 1967). Withasomnine is a pyrolo[1,2-b]pyrazole derivative that has been isolated from the roots of *Withania somnifera*, an indian medicinal plant (Schröter *et al.,* 1966). Nigellicine and nigellidine are pyridazinoindazolium alkaloids from *Nigella sativa* (Malik *et al.,* 1985).

The pyrazole ring emerged as an essential pharmacophore element when phenazone, one of the first analgesic and antipyretic drugs, was synthesized by Ludwig Knorr in 1883 (Apotrosoaei *et al.,* 2014). The pyrazole template was extensively used in the design of anti-inflammatory compounds (Nevagi, 2014), resulting molecules like lonazolac and trifezolac (Liu *et al.,* 2013). The development of non-steroidal anti-inflammatory drugs that directly targets COX-2 revealed the major role of the 1,5-diarylpyrazole moiety as central scaffold (Kumar *et al.,* 2013). Celecoxib is such a pyrazole derivative and it is used to treat the symptoms of osteoarthritis and rheumatoid arthritis (Goldenberg *et al.,* 1999).

The 1-(2,4-dichlorophenyl)pyrazole template emerged as a privileged structure for the development of cannabinoid receptor 1 antagonists. Rimonabant is the first pyrazole derivative used as an anorectic and antiobesity drug, although it has been withdrawn from the market due to potentially serious side effects (Lan *et al.,* 1999).

The pyrazole derivatives, and especially the aminopyrazoles, proved to be a useful pharmacophore scaffold in the design of various protein kinase inhibitors (Kumar *et al.,* 2013; Pal *et al.,* 2012). Tozasertib is a 3-aminopyrazole derivative and an anticancer chemotherapeutic pan-Aurora kinase inhibitor (Kim *et al.,* 2014). The usefulness of the aminopyrazole template can be observed in the structure of AT7519, a potent cyclin-dependent kinase inhibitor with antiproliferative activity on a large panel of human tumor cell lines (Ai *et al.,* 2010). Crizotinib is a pyrazole derivative acting as an inhibitor of anaplastic lymphoma kinase and of c-ros oncogene 1 inhibitor and it is approved for the treatment of non-small cell lung carcinoma (Shaw *et al.,* 2013).

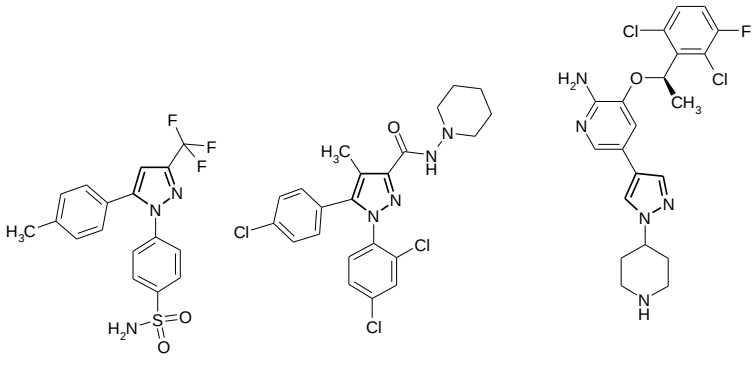

Fig. 1 Pyrazole-containing derivatives with various pharmacological activity

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Based on our previous research (Anuta *et al.*, 2014; Nitulescu *et al.*, 2013; Nitulescu *et al.*, 2012; Nitulescu *et al.*, 2010) focused on developing new pyrazole derivatives drugs, this study has the objective to analyze the pharmacological utility of the pyrazole scaffold and to assess his target-selectivity patterns. The research tries to answer the question if the pyrazoles as drug-like scaffolds are privileged structures for the protein kinases family or are promiscuous towards a plethora of various targets.

MATERIALS AND METHODS:

The data mining studies of compounds based on certain molecular scaffolds from large chemical databases is an important step in determining structure-activity relationships (Oprea *et al.*, 2012, Avram *et al.*, 2014). Reaxys database was used to link the chemical structures of the pyrazole derivatives with pharmacological targets, thus shaping the structure-target profile. It is a web-based chemistry database with a Medicinal Chemistry section containing over 5400000 substances and more than 26000000 bioactivity data points compiled from 320.000 medicinal chemistry publications and patents, fully indexed and normalized (Reaxys, 2014). The access to Reaxys database was granted by the UMF Carol Davila's Library and the study was performed in November 2014.

The Reaxys database was screen for any compound to have a pyrazole moiety in its structure. The results were filtered to remove the entries with mixtures of compounds. The compounds with insecticidal, pesticidal or herbicidal effects were filtered out and the final set was obtained. The subject of the study excluded the pyrazoline and pyrazolidine structures and their derivatives.

The structural set was analyzed in respect to its molecular descriptors distribution. In this study, we used the molecular weight (MW), the number of hydrogen bond donors (HBD), the number of hydrogen bond acceptors (HBA), and the number of rotatable bonds (RTB).

The pX querylet was used to filter a desirable range of affinity between the compounds and the targets. The pX value represents the logarithmic inverse value of any affinity measure, like inhibitory concentration 50% (IC50), efficacy concentration 50% (EC50), inhibition constant (Ki) or dissociation constant (Kd).

RESULTS AND DISCUSSION:

Molecular descriptors distribution

The average value of MW is 450 g/mol and the standard deviation is close to 100. About 73 percent of the data values are within one standard deviation of the mean. The correlation of this data with the low MW of the pyrazole ring (68 g/mol) indicates that it needs to be included in a bigger molecular framework in order to be pharmaceutically relevant. The graph of the MW values distribution for the pyrazoles derivatives takes a bell-shape curve and it is presented in figure 2.

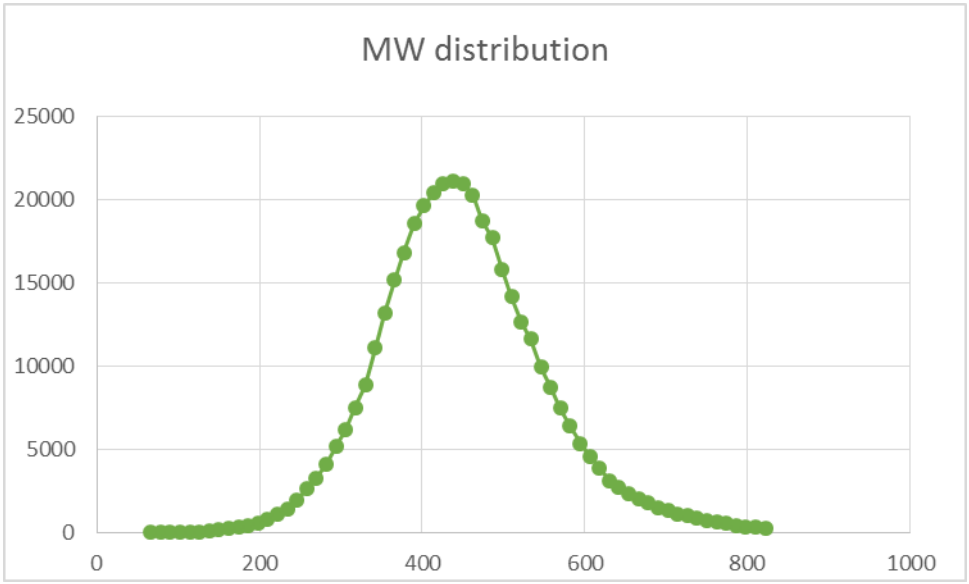

Fig. 2 The MW distribution of pyrazole derivatives

The analysis of the hydrogen bonding descriptors values indicates that most of the pharmaceutically active pyrazole derivatives have a HBD value lower or equal to 3. In comparison with the HBD values, the HBA descriptor has a wider range of values. The average value of HBA is close to 7 and 84% of the pyrazole derivatives in the working set have a HBA ranging from 4 to 9. The distribution curves are presented in the figure 3.

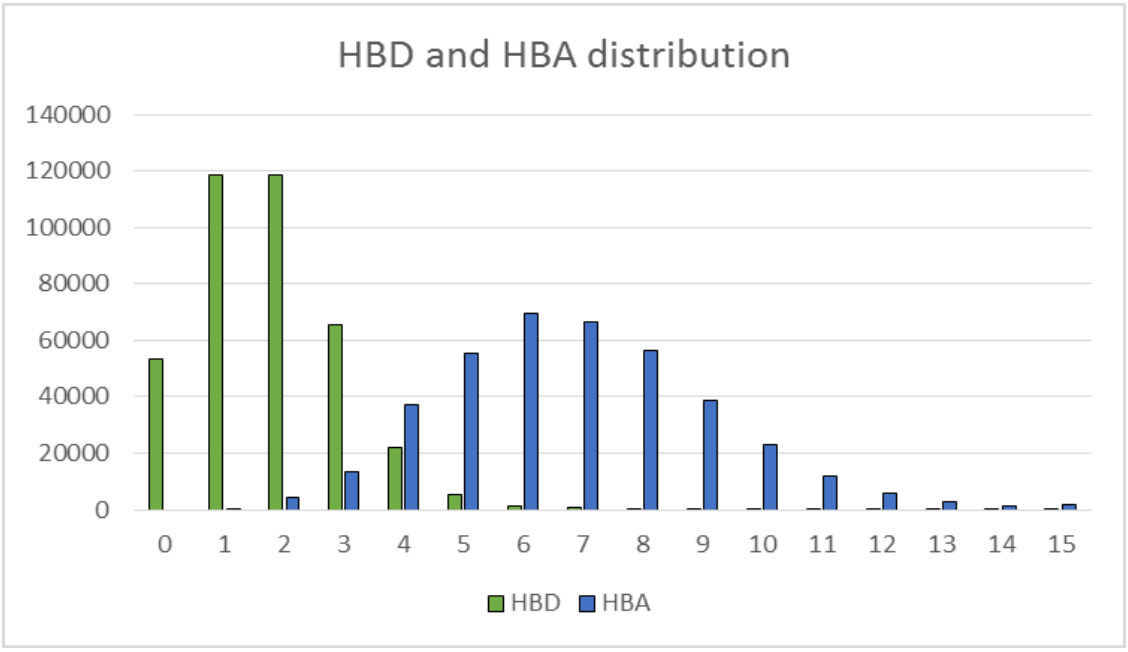

Fig. 3 The histograms of HBD and HBA distribution in pyrazole derivatives database

Rotatable bonds are defined as any single non-ring bond, bounded to nonterminal heavy atoms and their number represents a measure of molecular flexibility. The average RTB is close to 6. The distribution of the RTB descriptor in the set has a positive skewed curve and indicates the importance of a good molecular flexibility. The graphic representation of the corresponding histogram is similar to that of the MW distribution and is presented in figure 4.

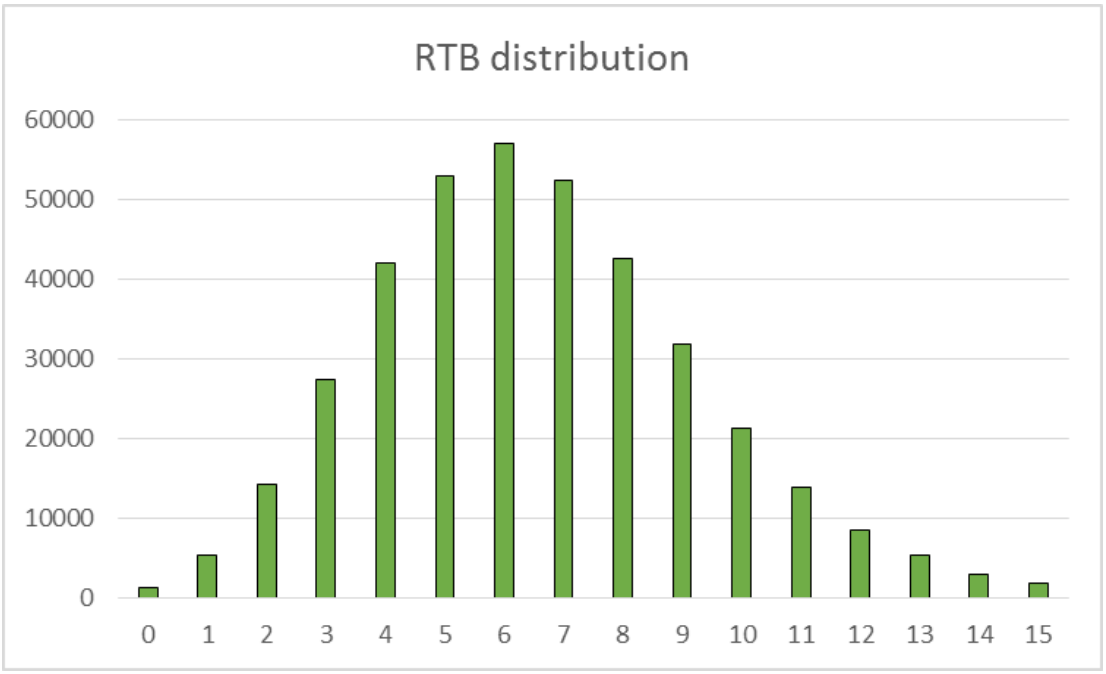

Fig. 4 The histogram of RTB distribution

The number of compounds that contain a fluorine (F), chlorine (Cl), bromine (Br), iodine (I) was also computed. The fluorine can be found in 36.8% of the compounds, the chlorine atom in 22.1%, the bromine in 3.4% and the iodine atom in only 0.4% of the compounds.

Target-selectivity patterns

After removing the non-drug profile compounds, the obtained set contains 403522 pyrazole derivatives cited in Reaxys to function on a number of 7771 targets. This high number of targets indicates the versatility of the pyrazole template and his usefulness in drug design. The Analysis View tool was used to measure the number of compounds to act on each target. In table 1, the number of compounds to interact with a certain target is presented in descending order.

Table 1.
The target profile of the pyrazole derivatives

No	Target	Target class	Count
1.	Vascular endothelial growth factor receptor 2 (vegfr2)	receptor tyrosine kinase	20024
2.	Aurora A kinase (aurA)	serine/threonine protein kinase	17248
3.	Cyclin-dependent kinase 2 (cdk2)	serine/threonine protein kinase	17119
4.	c-src kinase (csrc)	non-receptor tyrosine kinase	13287
5.	Janus kinase 2 (jak2)	non-receptor tyrosine kinase	12532
6.	Epidermal growth factor receptor (egfr)	receptor tyrosine kinase	11784
7.	Mitogen-activated protein kinase 14 (p38a)	serine/threonine protein kinase	11738
8.	Mitogen-activated protein kinase 1 (MAPK1)	serine/threonine protein kinase	11593
9.	Cannabinoid receptor type 1 (CB1)	G protein-coupled receptor	11485
10.	Insulin-like growth factor 1 receptor (Igf1r)	receptor tyrosine kinase	11424
11.	Phosphoinositide 3-kinase (pi3k)	phosphoinositide 3-kinase	10966
12.	Janus kinase 3 (jak3)	non-receptor tyrosine kinase	10333
13.	Hepatocyte growth factor receptor (met)	receptor tyrosine kinase	10275
14.	Tyrosine kinase with immunoglobulin-like and EGF-like domains (tie2)	receptor tyrosine kinase	10260
15.	Bcr-Abl tyrosine-kinase (abl)	non-receptor tyrosine kinase	9153
16.	Aurora B kinase (aurB)	serine/threonine protein kinase	9121
17.	Checkpoint kinase 1 (chk1)	serine/threonine protein kinase	9033
18.	Lymphocyte-specific protein tyrosine kinase (lck)	non-receptor tyrosine kinase	8879
19.	Glycogen synthase kinase 3 beta (gsk3beta)	serine-threonine kinase	8662
20.	Cyclin-dependent kinase 4 (cdk3)	serine/threonine protein kinase	8179
21.	Janus kinase 1 (jak1)	non-receptor tyrosine kinase	7890
22.	Spleen tyrosine kinase (syk)	non-receptor tyrosine kinase	7725
23.	Fms-like tyrosine kinase 3 (flt3)	receptor tyrosine kinase	7348
24.	Cyclin-dependent kinase 1 (cdk1)	serine/threonine protein kinase	7161
25.	MAPKAPK2 (MAP kinase-activated protein kinase 2)	serine/threonine protein kinase	6471

The analysis of the number of pyrazole derivatives registered to interact with a specific biological substrate, indicates the protein kinases class as a preferential target for these compounds. From all the 25 targets presented in the table, only 2 are not protein kinases: the cannabinoid 1 receptor and the phosphoinositide 3-kinase.

A number of 43495 pyrazole derivatives interact with receptor tyrosine kinases, 36604 with the non-receptor tyrosine kinases and 61862 with the serine/threonine protein kinases. Except for p38a and MAPKAPK2, all the protein kinases presented in the table 1 play central roles in cancer pathology, demonstrating the importance of the pyrazole ring in the development of antitumor drugs.

Within the receptor tyrosine kinases group analysed, a preferential target is represented by vascular endothelial growth factor and its receptors (vegfr), essential in physiological and pathological angiogenesis. Their inhibitors, such as axitinib (Verzoni *et al.*, 2014) and pazopanib (Sun *et al.*, 2014), which contain a pyrazole ring fused in an indazole scaffold, are approved as antiangiogenic tumor therapy in renal carcinoma.

Aurora A kinase and cyclin-dependent kinase 2, important cell cycle regulating enzymes, are the next frequent targets of the pyrazole derivatives. Their involvement in cell proliferation rendered these enzymes high-value targets for development of cancer therapeutics, with multiple inhibitors currently in early-phase clinical trials (Nikonova *et al.*, 2013; Endicott *et al.*, 2013).

In order to better evaluate the structural importance of the pyrazole ring and its framework, we filtered the initial set of compounds and isolated the structures containing fused/non-fused pyrazole ring. We analysed the target of profiles for both types of systems. The most frequent reported pyrazole fused systems were: indazole, pyrazolo[1,5-a]pyrimidine, pyrazolo[3,4-d]pyrimidine, pyrazolo[1,5-a]pyridine and pyrazolo[3,4-b]pyridine. The number of compounds interacting with a certain target are presented in descending order for each scaffold in table 2.

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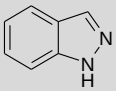
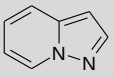
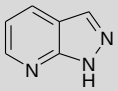
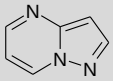
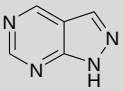
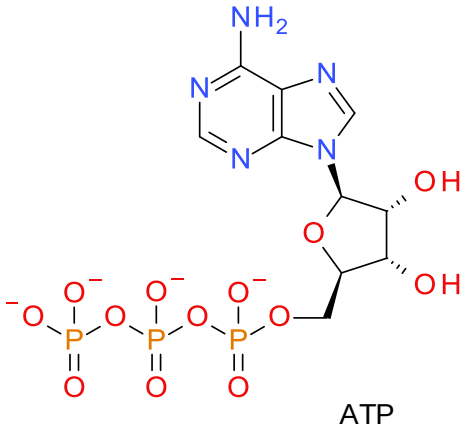
Table 2.
The target profile of the non-fused and fused pyrazole scaffolds

						
1.	jak2 8877	vegfr2 5299	A1 412	PDE4b 2292	cdk2 2039	pi3k 3474
2.	vegfr2 8812	cdk2 5058	jak3 377	PDE5a 1375	CRF1 1838	c-Src 3214
3.	aurA 8477	erk2 3886	mGluR5 365	PDE4d 1206	frap 1476	egfr 2801
4.	p38a 7769	aurA 3770	egfr 353	PDE3 967	jak3 1316	tie2 2429
5.	jak3 6886	chk1 3706	CRF1 342	pkca 942	chk1 1188	frap 2342
6.	met 6364	syk 3534	PDE4b 327	pkcd 934	jak2 1157	vegfr2 2341
7.	jak1 5778	lck 3395	erbb2 312	pkct 928	MAPKAPK 1019	abl 1881
8.	CB1 5659	tie2 3162	mark3 305	PDE6 888	mGluR5 818	pdgfr 1791
9.	aurB 5438	cdk4 3015	pi3k 274	pkcb 729	tyk2 671	lck 1385
10.	cdk2 5134	c-Src 2900	erbb4 273	pkcb ii 715	jak1 669	hck 1357
All	**201595**	**59162**	**6116**	**14934**	**24025**	**17019**

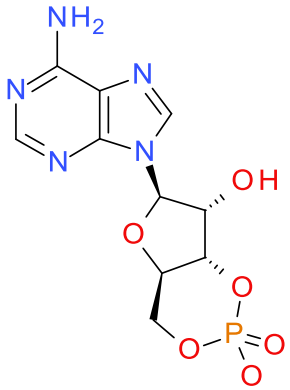
lck (*lymphocyte-specific protein tyrosine kinase*); A1 (*adenosine 1 receptor*); mGluR5 (*metabotropic glutamate receptor 5*); CRF1 (*corticotropin releasing factor receptor 1*), PDE (*phosphodiesterase*), erbb (*erythroblastic leukemia viral oncogene*), mark3 (*microtubule affinity-regulating kinase 3*); pkc (*protein kinase C*); pdgfr (*platelet-derived growth factor receptor*); hck (tyrosine-protein kinase HCK)

The analysis of the data presented in table 2 indicates that almost half of the compounds from the working set, share a non-fused pyrazole template and in the other half of derivatives, the pyrazole ring is fused with a wide variety of other cyclic compounds. The most used pyrazole fused ring is the indazole scaffold, representing up to 15% of the entire pyrazole set, followed by the pyrazolo[1,5-a]pyrimidine template.

A clear difference between the target profiles of each scaffold is noticeable. The frequency of occurrence of the top 10 targets interacting with derivatives constructed on fused or non-fused pyrazole scaffolds, reveals protein kinases to be the most targeted molecular substrates. Most of kinase inhibitors are ATP competitive and the pyrazole ring in their structure probably mimics the adenosine fragment of ATP (Garuti *et al.*, 2010).



ATP



cAMP

Fig. 5 The chemical structure of ATP and cAMP

The pyrazolo[1,5-a]pyridine scaffold proves to be very important in the structure of drugs aiming the adenosine receptors, probably because it is structurally equivalent with the adenosine molecule, the receptor's natural ligand. The pyrazolo[3,4-b]pyridine scaffold is largely used in the structure of various phosphodiesterase inhibitors. PDE inhibitors have been identified as new potential therapeutics in areas such as pulmonary arterial hypertension, coronary heart disease, dementia, depression, asthma or schizophrenia. The PDEs degrade the phosphodiester bond from

cyclic nucleotides, like cAMP and cGMP, being important regulators of signal transduction mediated by these second messenger molecules. The mechanism of PDE inhibition is similar to that described for the protein kinases inhibitors, the pyrazolo[3,4-b]pyridine fragment being used to mimic the cAMP or the cGMP structures.

The number and position of the nitrogen atoms in the 6-5 fused ring template are also decisive for the selectivity of pyrazole-based derivatives. For example, the pyrazolo[1,5-a]pyrimidine and his bioisoster, the pyrazolo[1,5-a]pyridine fragment, are important in the structure of non-peptide CRF1 antagonists, now in preclinical trials for treatment of several psychiatric disorders (Koob and Zorrilla, 2010).

Other molecular targets of compounds with pyrazole-based structure include cannabinoid receptor 1 and the metabotropic glutamate receptor 5.

To determine if the pyrazole scaffold is really necessary for a compound to interact with a particular target or not, we searched the Reaxys database for all the substances interacting with a certain target, at a pX value over 3, and calculated the number of compounds which contain in their structure the pyrazole scaffold. The results are presented in the table 3, as percent values.

Table 3.

Number (%) of pyrazole based compounds to interact with a specific pharmaceutical target

No	Target	%
1	Aurora B kinase	49
2	Mitogen-activated protein kinase 1	48
3	Aurora B kinase	42
4	Checkpoint kinase 1	33
5	Cyclin-dependent kinase 2	29
6	Insulin-like growth factor receptor 1	27
7	Tyrosine kinase with immunoglobulin-like and EGF-like domains	27
8	Cannabinoid receptor 1	24
9	Phosphoinositide 3-kinase	23
10	Mitogen-activated protein kinase 14	23
11	Vascular endothelial growth factor receptor 2	22
12	Janus kinase 2	21
13	Cyclin-dependent kinase 4	17
14	Lymphocyte-specific protein tyrosine kinase	15
15	Epidermal growth factor receptor	14

This analysis reveals the high importance of the pyrazole scaffold in the development of the Aurora B inhibitors, up to 49% of them containing in their structure this framework. The pyrazole fragment is also important in the development of other kinases inhibitors, especially from the serine/threonine protein kinase class, such as MAPK1, Aurora A or Chk1.

The pyrazole ring is a well-established framework in the development of drugs capable of interacting with the cannabinoid receptor 1, but it doesn't seem to be essential, only 24% of these substances containing this fragment.

The correlation of this data with the distribution of the molecular descriptors shows that the pyrazole ring may be important for a certain target, but it needs a bigger framework in order to have a molecular weight in the range of 300 to 600 g/mol, a good molecular flexibility and the proper number of hydrogen bonds donors and acceptors in order to be pharmaceutically relevant.

CONCLUSIONS:

Using data mining techniques, we demonstrated that pyrazole moieties provide selectivity towards several molecular substrates, giving the proper structural elements. The most important targets belong to the protein kinases family. Within this group, the pyrazole fragment proves to be an essential element in the structure of Aurora B, Aurora A kinases, MAPK1, and Chk1 inhibitors, further development of such compounds benefiting from the use of these moieties.

An underlying mechanism of pyrazole containing compounds involves structural equivalency with purines such as adenosine and its derivatives AMPc, ATP. Nevertheless, the usefulness of pyrazole template can be extended to obtain compounds which target other types of molecular substrates such as cannabinoid receptor 1, the metabotropic glutamate receptor 5 or the corticotropin releasing factor receptor.

Our conclusion is that pyrazole represents a privileged scaffold only if included in the proper framework. Varying substituents on the pyrazole scaffold can lead to the development of potent and selective binders for multiple biological targets, inhibitors with possible medical relevance for several important therapeutic areas.

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