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Extreme modulation properties of aromatic fluorine

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ABSTRACT

Thorough examination of the current literature as well as publicly available databases allowed us to qualify aromatic fluorine as a unique modulator of biological properties of organic compounds. In some rare cases, introduction of fluorine increased biological activity 100,000 times and even higher. We have also identified several examples where aromatic fluorine substantially reduced biological activity. Selected individual cases of extreme modulation are presented and discussed in the paper.

1. Introduction

Since the late 1950s, there has been a steady increase in the relative number of fluorinated biologically active compounds in active use, primarily in agriculture and in medicine. Statistical analysis of available data indicates that, on average, the proportion of fluorinated molecules among FDA approved drugs has gone up from about 7% to about 15% (Fig. 1).

This phenomenon has drawn the attention of many researchers and has been the subject of several review articles during the last 20 years [1–13]. One early hypothesis explained the enhanced biological activity of fluorinated compounds as being due to increased lipophilic properties of fluorinated molecules. The underlying basis of this hypothesis was later somewhat eroded with the discovery of several notable examples where the introduction of fluorine actually reduced lipophilicity of compounds [14]. More recent review of available X-ray databases allowed identification of both fluorophoric and fluorophilic areas in active centers of proteins. This discovery provided a partial explanation of the phenomenon via the acknowledgement of the specific ligand–target interactions mediated by fluorine [6]. Other proposed hypotheses include "polar hydrophobicity", "transition state analogs", "limited H-bond acceptor", "orthogonal multipolar C–F···C=O interactions", "fluorinated aromatic quadrupolar interactions", "C–F···X dipolar interactions", "stereoelectronic interactions", "trajectory-dependent n–π* interactions", "electrostatic/dipole interactions", and other ideas [2–14]. While it is clear that several, if not all, of the above mentioned hypotheses need to be taken into consideration to explain the mode of action of fluorinated ligands, perhaps the most likely explanation is the extreme electronegativity of fluorine atom leading to strong, specific dipole-type interactions between a ligand and a target within an active center of a protein molecule.

The recent advent of high throughput synthesis and biological screening opened up another venue to explore effects of fluorine on biological activity. Here we present the results of our analysis of available literature data and publicly available databases regarding the biological activity of fluorinated compounds in direct comparison with their non-fluorinated analogs, as well as with other halogen atoms, such as chlorine and bromine.

2. Results and discussion

An initial analysis was performed on the public domain NCI database [15,16]. To prevent complications in the interpretation of results, only non-ionic individual molecules with established chemical structures were taken into consideration, providing the initial set of 35,645 compounds. Evaluation of this database

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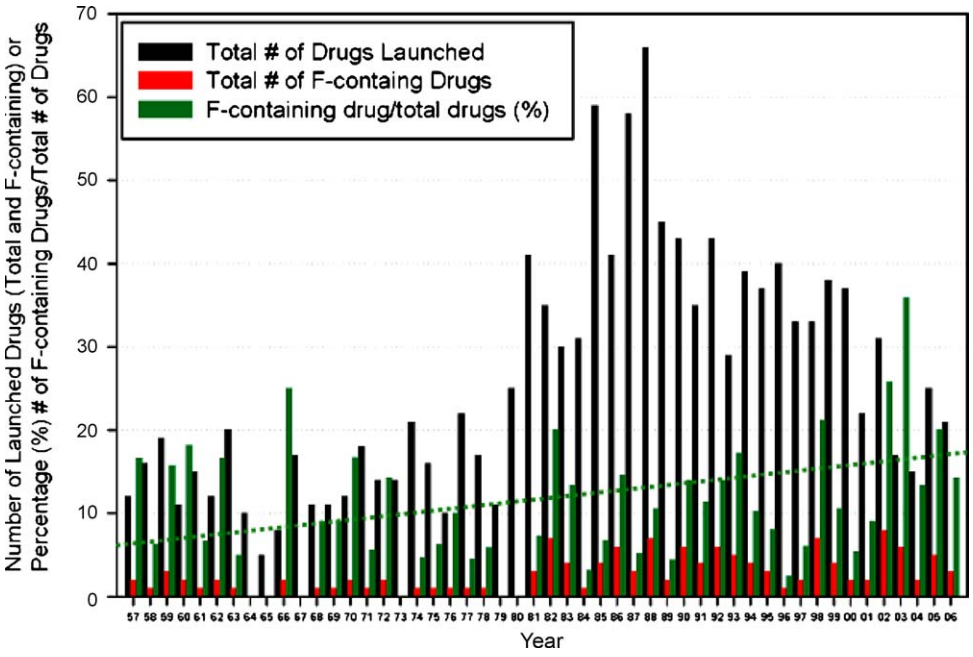

Fig. 1. Chronological occurrence of fluorinated drug molecules.The graph was adapted from [1].

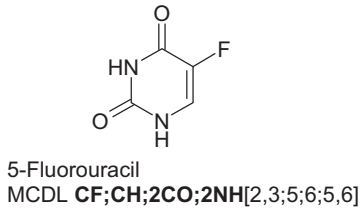

Fig. 2. Chemical structure and MCDL linear descriptor of 5-fluorouracil.

indicated that introduction of fluorine slightly improves the chances of finding an active compound. Thus, among all 35,645 compounds, 804 compounds, or 2.23%, had one aromatic fluorine atom, whereas among a subset of 1237 "active" compounds with pGI50 > 6.0, 32 compounds, or 2.56%, had one fluorine atom. (pGI50 is the −log of the molar concentration of a compound causing 50% growth inhibition of cancer cells.) These relative numbers, 2.23% and 2.56% are different by 16%, which is a relatively modest improvement. Unfortunately, direct comparison of fluorine effects with those of other halogens, such as chlorine and bromine, was not possible due to lack of corresponding comparison pairs among the compounds in the NCI database.

Further evaluation of the available NCI data was made using Free–Wilson [17] analysis based on the MCDL fragment approach [18,19]. (Free–Wilson analysis is a variant of QSAR which assumes that in the parent structure each variable fragment contributes additively to the logarithm of biological activity, and there is no interaction between the fragments.) Initially, the 35,645 compound set was converted to MCDL strings using the MCDL Java Editor [19]. Only the composition MCDL modules (bold, Fig. 2) were used for subsequent computations.

In the set of 35,645 compounds, nine MCDL fragments occur more than 10,000 times: CH, C, CHH, CHHH, CO, N, O, NH, and OH. A second set occurs between 1000 and 10,000 times: S, CCl, NHH, CN, NOO, SOO, CS, CBr, CFFF, and CF. Aromatic fluorine (CF fragment) belongs to this group with the occurrence rate of 1417. The least frequent MCDL fragments have occurrence rates below 100. Only about 1% of all compounds have one of these rare fragments, even though they represent almost half of all fragments (Table 1).

The results of a Free–Wilson calculation, using singular value decomposition (SVD), on a subset of 35,389 compounds with pGI50 ≥ 4.0 and several prominent MCDL fragments including aromatic fluorine CF are presented in Fig. 3 and Table 2. These results confirmed our previous observations that the presence of aromatic fluorine somewhat positively affects the overall

Table 1
Occurrence rates of MCDL fragments in the NCI dataset of 35,645 compounds.

Fragment	Rate	Fragment	Rate	Fragment	Rate	Fragment	Rate	Fragment	Rate
CH	272,621	NOO	3235	Cl	194	CBrBr	21	SFOO	3
C	175,536	SOO	3038	CBrH	177	CClClH	18	CBrF	2
CHH	95,492	CS	2375	CFF	154	I	17	CClO	2
CHHH	61,789	CBr	1495	CBrHH	152	CFFH	11	NBr	2
CO	49,192	CFFF	1418	CClCl	145	PHO	10	PH	2
N	47,987	**CF**	**1417**	P	138	CBrBrH	8	CBrBrBr	1
O	41,204	PO	810	CClClCl	77	CBrCl	8	CClClF	1
NH	26265	NO	713	CClFF	66	CHS	6	CHII	1
OH	20,303	CClHH	479	PS	43	CII	6	NI	1
S	8147	CHO	475	CFH	37	CBrI	5	NN	1
CCl	7489	SH	399	CHHI	28	PClCl	5	NS	1
NHH	5027	CClH	269	CFHH	27	NCl	3	PCl	1
CN	3375	SO	249	CHI	22	NF	3	NI	1

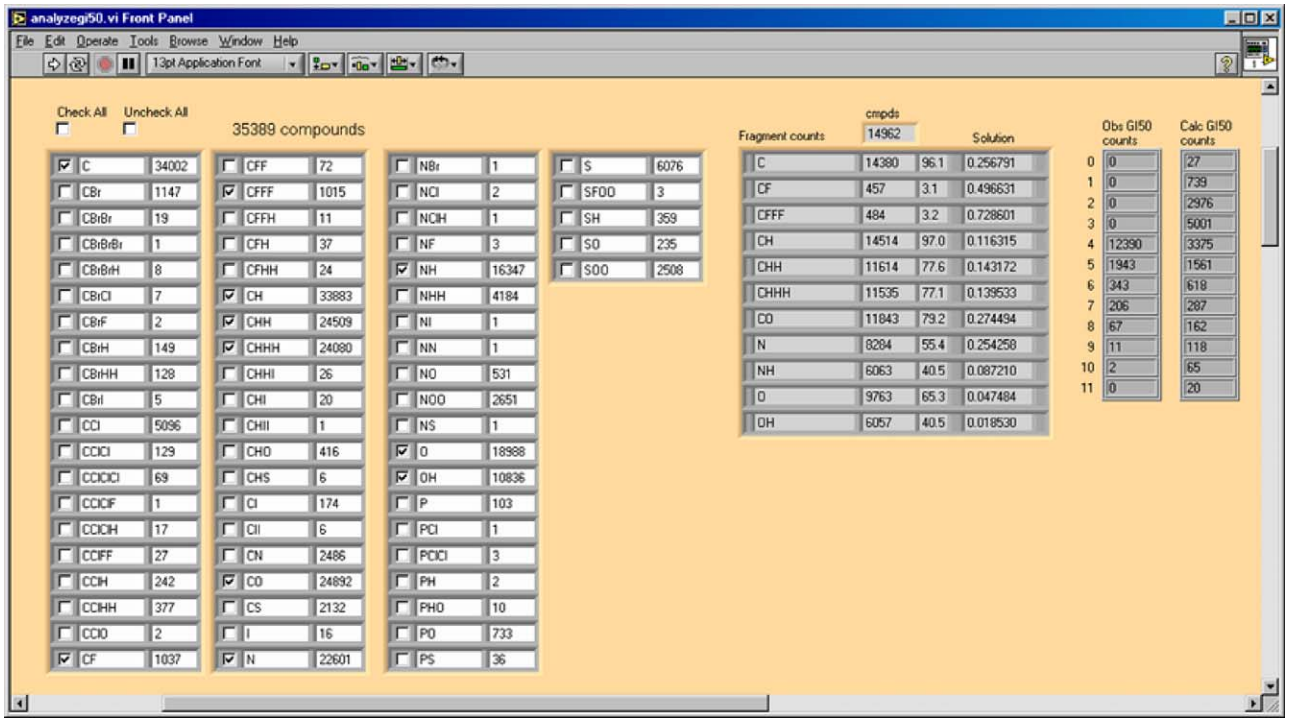

Fig. 3. Free–Wilson analysis of the NCI dataset.

biological activity of organic compounds, albeit on a moderate scale. According to the Free–Wilson analysis, replacement of CH fragment with CF fragment is expected to improve activity by +0.38 (in pGI50 units). The actual average observed improvement is smaller (+0.09, see below), a reflection of the limitations of the linear additive approximation in the Free–Wilson analysis.

Finally, the effect of aromatic fluorine was evaluated using the results of high throughput biological activity screening presented in 167 individual papers, which were randomly selected from the two leading medicinal chemistry journals, the ACS *Journal of Medicinal Chemistry* and *Bioorganic & Medicinal Chemistry Letters* using "fluorine" as the search keyword. In these 167 papers we were able to identify 425 unique CH/CF compound pairs where the effect of aromatic fluorine on biological activity can be compared directly.

Initial analysis showed that in these 425 pairs of compounds the replacement of the aromatic CH fragment with the CF fragment resulted in an increase of biological activity for 222 compounds (52%), a decrease of activity for 196 compounds (46%), and did not change activity within the experimental error for the remaining 7 compounds (2%). The overall average improvement of biological activity (as represented by pGI50 or relevant pIC50 and pEC50 values) was moderately positive, +0.09, which corresponds to 24% improvement in activity on a non-logarithmic scale. (Similar to pGI50, pIC50 is −log of 50% inhibitory concentration, and pEC50 is −log of 50% effective concentration.) These results are in general agreement with the previously discussed analysis of the NCI data set.

Further insight into the mode of biological action of aromatic fluorine was achieved by the investigation of the distribution curve of biological activity modulation among these 425 pairs. We found that in 32 cases the activity was improved more than 10 times compared to 20 cases where activity was decreased more than 10 times. We also found that in 12 cases introduction of fluorine improves the biological activity more than 100 times, and only 3 cases where introduction of fluorine decreases the biological activity more than 100 times. In 4 cases biological activity was improved more than 1000 times, and in 2 cases more than 100,000 times. Aromatic fluorine is also capable of substantially decreasing biological activity, in one particular case more than 1000 times (Fig. 4). Our preliminary analysis of similar cases involving aromatic chlorine and aromatic bromine taken from the same journals indicated that none of these positive extreme results is observed with these halogens.

5-Fluorobenzothiazoles, such as 2-(3,4-dimethoxyphenyl-5-fluorobenzothiazle (NSC 721648, **8n** in Fig. 5) are significant examples of aromatic fluorine's ability to modulate anti-cancer activity in a dramatic fashion [20,21]. These benzothiazoles **8** are somewhat unusual not only because of the very strong positive fluorine effect (fluorinated compound **8n** is 170,000 times more active than non-fluorinated compound **8c** and 19,520 times more active than the chlorinated analog **8v** against HCC-2998 human colon cancer cell line; **8n** is more than 500,000 times more active than **8c** against MCF-7 human breast cancer cell line), but also because of a rare cell type selectivity. For example, **8n** is more than 1000 times more active against HCC-2998 compared to KM-12, which are both human colon cancer cell lines [20].

Unfortunately, little is known about the specific enzyme target of 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (**8n**), and the molecular mechanism(s) of action responsible for this unique cell type selectivity. It was demonstrated that, unlike other compounds

Table 2
Free–Wilson (FW) contributions of some prominent MCDL fragments in comparison with CF fragment, in pGI50 units.

Fragment	**CH**	C	CHH	CHHH	CO	N	O	NH	OH	**CF**
FW contribution	**0.12**	0.26	0.14	0.14	0.27	0.25	0.05	0.09	0.02	**0.50**

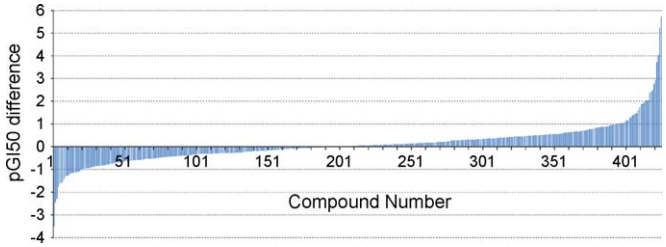

Fig. 4. Distribution curve of aromatic fluorine modulation of biological activity of 425 compound pairs from the 167 individual papers discussed above. Note the *Y* axis is a logarithmic scale, so each unit represents a 10-fold change of the activity.

of this class, **8n** is capable of induction of cell cycle arrest at the G2/M phase and can inhibit aryl hydrocarbon receptor (AhR) at nanomolar concentrations [21]. It is also important to note that the above mentioned dramatic fluorine effect has not been observed in 2-phenylbenzimidazoles or in 2-phenylbenzothiazoles with different phenyl group substituents, such as methyl and amino groups, even though fluorinated 2-phenylbenzothiazoles are generally much more active than non-fluorinated ones [20–22].

Additional examples of the positive aromatic fluorine effect include indenoisoquinolines as Topoisomerase I inhibitors (Fig. 6). Similar to fluorobenzothiazoles **8**, the molecular structures of the complexes of these indenoisoquinolines with Topoisomerase I are not known, so it is difficult to judge why fluorinated indenoisoquinolines presented in Fig. 6 are substantially more active than their non-fluorinated analogs. It is interesting to note that the replacement of the azido group in a remote position with an ammonium fragment rendered this difference between fluorinated and non-fluorinated molecules in an opposite direction while simultaneously improving the overall activity [23]. A trivial assumption that this amino group is bonded in the same part of the active center as the CF fragment is highly improbable given the stereochemical as well as physical–chemical considerations. It was never documented in the available literature that an aromatic CF fragment and an aliphatic ammonium cation could participate in competitive binding to the same part of the active center. More importantly, other favorable interactions would have to be altered substantially for this competitive binding to occur. A more likely hypothesis is that there is a strong binding site for this ammonium cation in the active center of Topoisomerase I. This strong binding distorts the relative active center position of the CF fragment in ammonium salt **68** compared to the azide **56**, so the CF fragment in **68** can no longer participate in any favorable interactions within the active center.

Somewhat better understanding of the positive modulation properties of the aromatic fluorine can be achieved using the results of the recent study of aryl(hetaryl) disubstituted pyrazoles [24]. These compounds are classical examples of A–B–C heterocyclic systems [25–27]. The authors of the study [24] were able to determine the X-ray structure of the 4-hydroxy derivative of the parent compound **15** bound to the ATP-binding site of the TβR I kinase domain (Fig. 7). In this complex the 4-hydroxy group was involved in a hydrogen bonding interaction as a hydrogen bond acceptor. In addition, this 4-hydroxy derivative is significantly more active than the parent compound **15**. The correlation

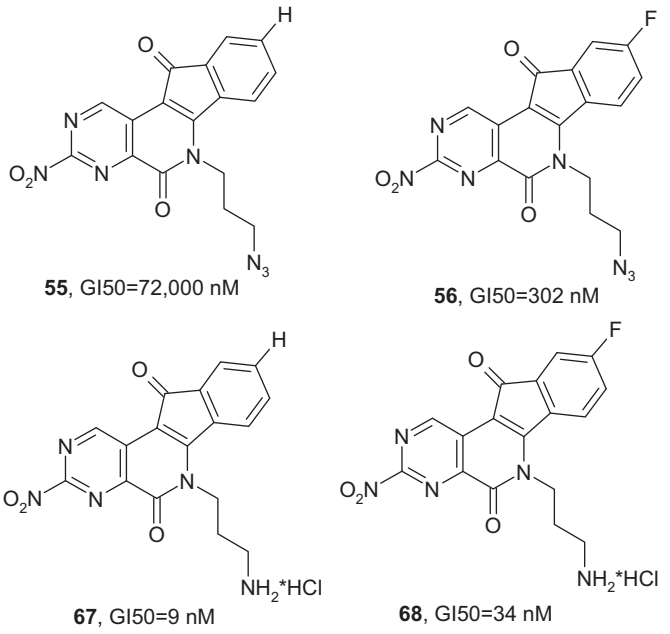

Fig. 6. Chemical structures and biological activity (against SN12C human renal cancer cell line) of indenoisoquinolines [23]. The original numeration of [23] was retained for cross-reference.

between the hydrogen bonding and activity was further confirmed by evaluation of a 4-methoxy derivative which is also more active than the parent compound **15**. It is reasonable to assume that the positive aromatic fluorine effect in the 4-fluoro derivative **16** can be attributed to the weak hydrogen bond acceptor properties of the fluorine atom. The weak hydrogen bond acceptor properties of aromatic fluorine are well documented (see, for example [28]).

Like any potent modulator, aromatic fluorine can not only increase, but also decrease the potency of drug-like molecules. This decrease usually can be attributed to specific unavoidable destabilizing interactions between the CF fragment and the target protein in otherwise partially optimized drug molecules where other functional fragments lock the molecule tightly in a binding site. COX-2 inhibitors, which belong to the 3,4,6-triphenylpyran-2-one class, represent a good example of such unavoidable interactions [29].

The unsubstituted phenyl group in **12e** is neatly oriented toward a hydrophobic pocket created by Leu, Tyr, and Trp units of COX-2 protein (Fig. 8). Introduction of a fluorine atom in the 4-postion of this phenyl ring induces a substantial dipole moment and disrupts the favorable interactions in this hydrophobic pocket. These unfavorable interactions cannot be relieved by re-orientation of the molecules since this will disrupt other favorable interactions provided by two additional functional fragments of the molecule, OMe and SO_2Me groups. As a result, the fluorinated analog **12h** is more than 50 times less potent than the non-fluorinated one. An even more dramatic difference was observed in the case of the OEt analog of **12e** (not shown) where introduction of aromatic fluorine in the 4-postion reduced the biological activity more than 3000 times.

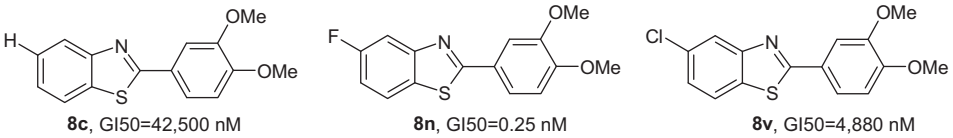

Fig. 5. Chemical structures and biological activities (against HCC-2998 human colon cancer cell line) of (3,4-dimethoxyphenyl)benzothiazoles [20]. The original numeration of [20] was retained for cross-reference.

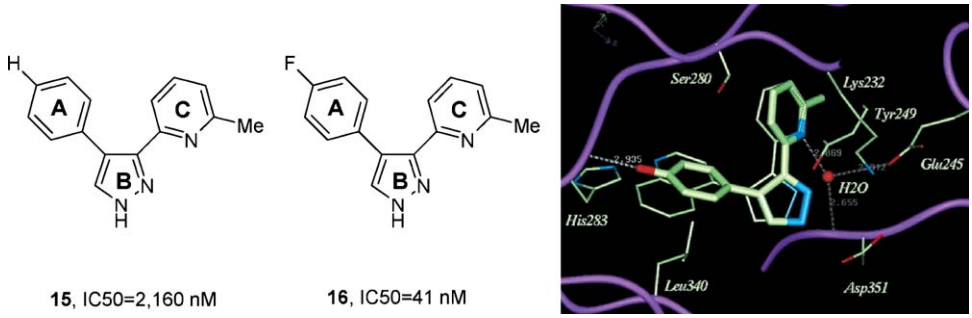

Fig. 7. Chemical structures and biological activities (TGF-β RI kinase, NIH 3T3 assay) of aryl(hetaryl) disubstituted pyrazoles **15** and **16** (left); r-Ray structure of the 4-hydroxy derivative of the parent compound **15** bound to the ATP-binding site of the TβR I kinase domain (right, adapted from the Ref. [24]). The original numeration of [24] was retained for cross-reference.

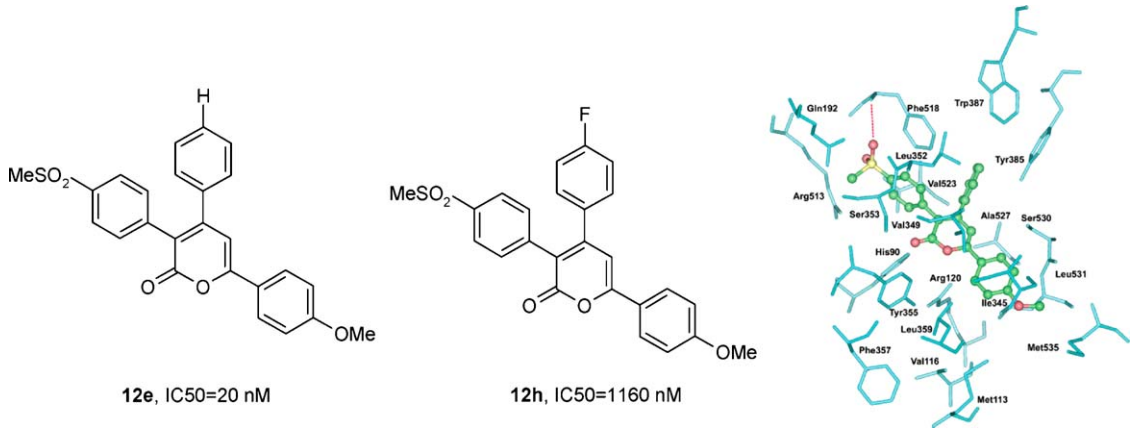

Fig. 8. Chemical structures and biological activities of **12e** and **12 h** (left); docking of **12e** in the active site of COX-2 (right, adapted from Ref. [29]). The original numeration of [29] was retained for cross-reference.

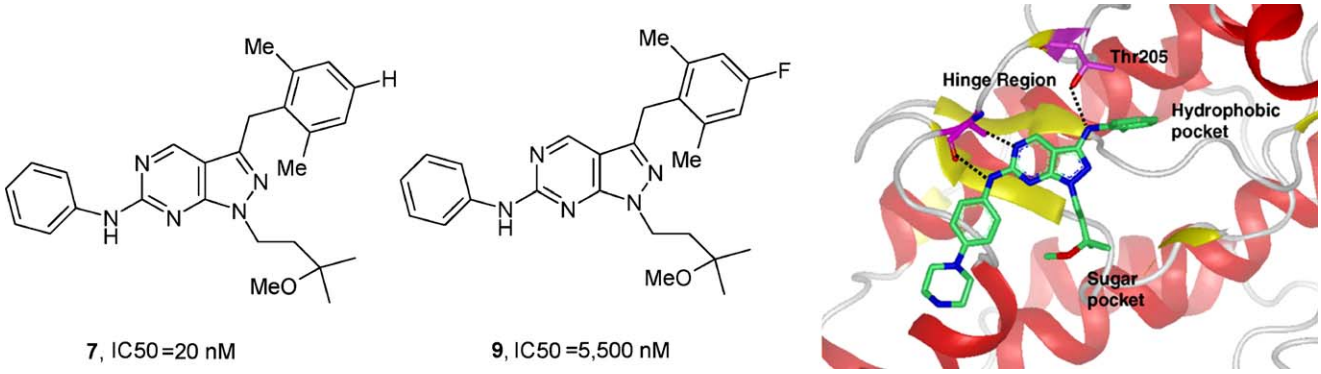

Fig. 9. Chemical structures and biological activities of non-fluorinated and fluorinated N^3,N^6-diaryl-N^6-(3,3-dimethyl-3-methoxypropyl)pyrazolo[3,4-d]pyrimidine-3,6-diamines **7** and **9** (left); docking of the corresponding 4-piperazin-1-yl derivative in the active site of ACK1 (right, adapted from Ref. [30]). The original numeration of [30] was retained for cross-reference.

Another interesting example of significant negative modulation of biological activity also probably involves unfavorable hydrophobic pocket interactions [30]. In this case the dimethyl-phenyl group of compound **7** is positioned in the vicinity of a hydrophobic pocket (Fig. 9). Introduction of fluorine in the 4-postion of this dimethyl-phenyl group leads to a significant decrease in activity (almost 300 times). Again, like in the previous case, the rest of the molecule is tightly bound in the active site via a network of hydrogen bonds involving pyrimidine nitrogen and NH groups [30]. In this situation re-orientation of the molecule to avoid the undesirable proximity of the CF fragment to the hydrophobic pocket is not feasible since this re-orientation will result in disruption of the already energy-optimized hydrogen bond network.

3. Conclusions

The presented data and analysis clearly indicate that aromatic fluorine, while only marginally improving the average biological activity of organic compounds in general, can act as a strong activity modulator in some specific cases. We found examples where introduction of aromatic fluorine improved biological potency by 4–5 orders of magnitude. This was not observed in the more limited subset of aromatic chlorine and bromine compounds evaluated within the same data set [31]. We also found that the introduction of aromatic fluorine in the vicinity of hydrophobic pockets could significantly reduce activity, presumably due to the known dipole properties of the CF fragment. Since

only aromatic fluorine compounds were studied in the current analysis, we can make no conclusions about the modulation properties of aliphatic fluorine. However, we have so far found nothing to indicate that the extreme modulation properties of fluorine are limited to aromatic compounds.

4. Note added in proof

Detailed analysis of the existing literature data lends some credence to the idea of structure dependence on the modulation properties of aromatic fluorine. For example, the two analyzed examples [29,30] where introduction of fluorine in the *para* position of the terminal benzene rings resulted in substantial loss of activity are probably not incidental. We subsequently performed thorough evaluation of a representative set of compounds from the public domain ChEMBL database [32] where a fluorine atom was introduced in the *para* position of an unsubstituted terminal benzene ring (see compounds **12e** and **12h** above as an example). Out of 140 cases, introduction of *para* fluorine resulted in a substantial (more than 10-fold) reduction of biological activity 11 times, and in a substantial increase of activity only 1 time. In this particular molecular environment fluorine acts as a negative modulator. The structure dependence of modulation properties was also reported for other fluoroaromatic compounds [33]. Full analysis of structure-specific modulation properties of fluorine will be presented elsewhere.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2010.11.009.

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