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Letter

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Fluorine Scanning by Nonselective Fluorination: Enhancing Raf/MEK Inhibition while Keeping Physicochemical Properties

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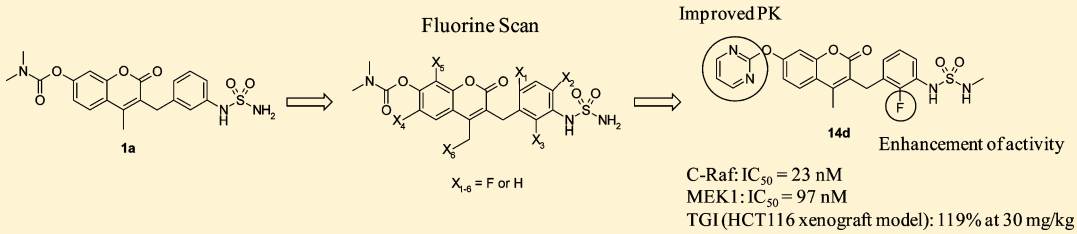
Supporting Information



ABSTRACT: A facile methodology effective in obtaining a set of compounds monofluorinated at various positions (fluorine scan) by chemical synthesis is reported. Direct and nonselective fluorination reactions of our lead compound **1a** and key intermediate **2a** worked efficiently to afford a total of six monofluorinated derivatives. All of the derivatives kept their physicochemical properties compared with the lead **1a** and one of them had enhanced Raf/MEK inhibitory activity. Keeping physicochemical properties could be considered a benefit of monofluorinated derivatives compared with chlorinated derivatives, iodinated derivatives, methylated derivatives, etc. This key finding led to the identification of compound **14d**, which had potent tumor growth inhibition in a xenograft model, excellent PK profiles in three animal species, and no critical toxicity.

KEYWORDS: *Fluorine scan, Raf, MEK, kinase inhibitor, anticancer*

A fluorine atom substitution of a hydrogen atom attached to a carbon atom (fluorine substitution) has been intensively utilized to adjust molecular properties in many fields.[1−3] In the area of medicinal chemistry, fluorine substitutions of a lead compound are one of the most utilized modifications during lead optimizations,[4−7] and about 20% of marketed drugs contain fluorine atoms.[6,8] By fluorine substitution at appropriate positions, adjustments to the acidity or basicity of functional groups such as the hydroxyl and amino groups have been reported to improve permeability.[4,7,9] A fluorine block of metabolically unstable hydrogen can improve the metabolic stability.[7] Enhanced binding affinity to the target protein was also reported especially when X-ray crystallography was available and the particular positions of fluorination could be anticipated.[10,11]

The effects of fluorine substitution could vary depending on the presence or absence of subsets of neighboring functional groups. When such functional groups are located in proximity to the introduced fluorine, changes in 3D conformation resulting from electronic repulsions and/or changes in properties such as basicity can be derived. Conversely, if there are no such functional groups in the vicinity, of all chemical modifications, changes in 3D conformation would be minimal and those of electronic properties would also be limited.[5,12,13]

In the latter situation, one of the possible advantages of fluorine substitution is that the changes in physicochemical parameters (water solubility, membrane permeability, metabolic stability, etc.) could be minimal because of the limited changes in 3D and electronic structures. In fact, fluorine substitution could solve the paradox often encountered in medicinal chemistry that a derivatization favorable for one factor (bioactivity, physicochemical properties, toxicity, etc.) derives unacceptable change for another factor in developing a clinical candidate. Fluorine substitution has the potential to improve bioactivity with the essence of the drug untouched.

Various synthetic methodologies to introduce fluorine were reported including regioselective and enantioselective reactions.[14−16] These methods are powerful when the target

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position for fluorination has been identified. However, exhaustive reaction steps are required when the target position is unknown, and random scanning of fluorinated positions is used to identify the best. An effective method for a fluorine scan was reported in 2009 using mutant CYP metabolism,[17] but to the best of our knowledge, there are no reports of facile chemical methodologies effective for fluorine scanning.[18] We previously reported that compound CH5126766/RO5126766 showed both Raf and MEK inhibitory activity of the Ras/Raf/MEK/ERK pathway, and it showed superior antitumor effect compared to that of a pure MEK inhibitor in a mouse xenograft.[19−21] Here we report the facile strategy of a fluorine scan utilized during our hit-to-lead chemistry, and the excellent effects of monofluorination on the bioactivity of our lead while retaining its physicochemical properties.

To achieve a fluorine scan of a lead, we chose the direct and nonselective fluorination reaction of a lead compound (or a key intermediate) (Figure 1). Usually selective chemical reactions

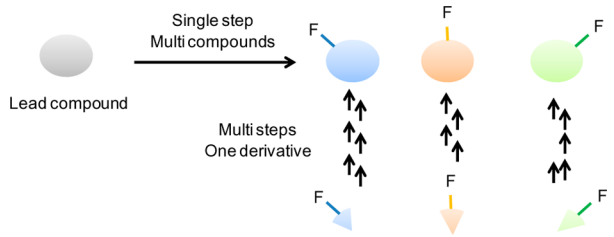
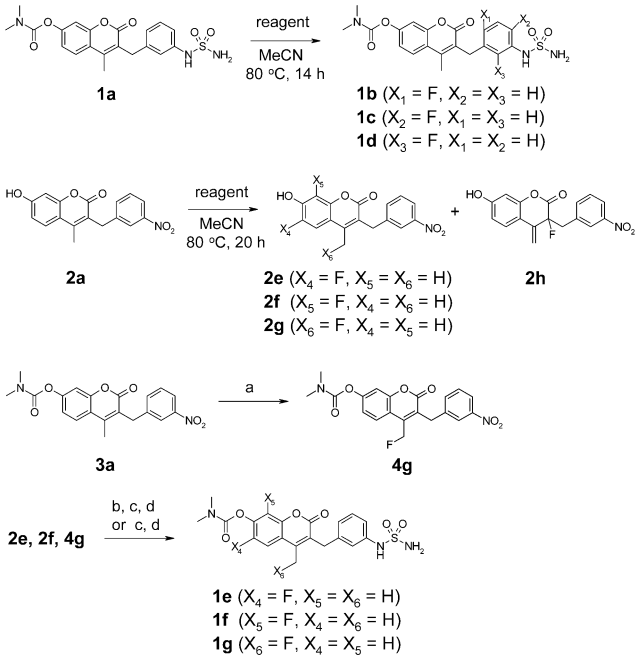


Figure 1. Fluorine scanning by direct and nonselective monofluorination or stepwise synthesis.

to afford only one derivative are preferable, but this method of stepwise chemical synthesis requires multisteps to obtain only one derivative, and exhaustive chemical steps need to be conducted to achieve fluorine scanning. In contrast, the advantage of the nonselective method is that a single reaction could afford several compounds. Direct fluorination of a lead is a powerful method for two reasons: it can be applied to compounds with a set of functional groups, and many fluorination reagents are commercially available,[14] so the desired nonselectivity could be achieved by fine-tuning the reactivity for each reactant.[22,23]

Fluorination of lead compound **1a**[21] and key intermediate **2a**[21] afforded a total of six monofluorinated derivatives (Scheme 1; **1b**, **1c**, **1d**, **2e**, **2f**, and **2h**). Because fluorination of lead **1a** by reagent **5** did not proceed (entry 1), we chose the more reactive reagent **6**. This afforded compound **1b** in a selective manner (entry 3). However, reagent **7**, which has the highest reactivity among the three reagents, afforded the three monofluorinated compounds in a nonselective manner (ratio of **1b**/(**1c** + **1d**) = 32/26 (entry 5)), and isolated yields after chromatography were 15% (**1b**), 4.3% (**1c**), and 3.4% (**1d**). Fluorinated positions of these three compounds were identified (see Supporting Information) by their coupling pattern in ^{1}H NMR (discrimination of **1d**,[24] from **1b** and **1c**), and correlation in CH-HMBC spectrum (discrimination of **1b** and **1c**). For key intermediate **2a**, nonselective monofluorination was achieved by reagent **6**, while the more reactive reagent **7** gave only multifluorinated compounds (entry 6). The fluorinated intermediates **2e** and **2f** were further modified to targets **1e** and **1f** by 3 steps as shown in Scheme 1 in a total isolated yield of 2.5% and 2.8%, respectively, from intermediate **2a**. Fluorinated positions of **1e**[24] and **1f** were discriminated by

Scheme 1. Direct and Nonselective Monofluorination[a,b,c]



entry	reagent	(eq.)	substrate	ratio[b] (%) 2e	2f	2h	1b	1c + 1d
1	 5	(2.0)	**1a**	-	-	-	1.0	<0.1
2		(2.0)	**2a**	<0.1	<0.1	<0.1	-	-
3	 6	(1.0)	**1a**	-	-	-	27	<1
4[c]		(1.0)	**2a**	13	17	1.2	-	-
5	 7	(2.0)	**1a**	-	-	-	32 (15)	26 (**1c**: 4.3, **1d**: 3.4)
6		(2.0)	**2a**	<0.1	<0.1	<0.1	-	-

[a]Reagents and conditions: (a) LiHMDS (1.0 equiv), THF, −78 °C, 30 min, then, **5**, 2 h, 53%. (b) *N*,*N*-dimethylcarbamoyl chloride (1.2 equiv), NaH (1.1 equiv), THF, rt, 1 h; (c) $SnCl_2$ (5.0 equiv), EtOH/EtOAc 1:1, 80 °C, 3 h; (d) chlorosulfonyl isocyanate (2.7 equiv), HCOOH (1.3 equiv), pyridine (2.0 equiv), CH_2Cl_2, rt, 16 h. [b]The ratio of **2e**−**h** was determined by HPLC analysis (UV area% at 200−400 nm) using 2,4-difluoro-nitrobenzene as an internal standard. The ratio of **1b**−**d** was determined by LC/MS analysis (MS area%) taking **1a** intensity before the reaction started as 100%. The peaks of **1c** and **1d** overlapped. Isolated yields are described in parentheses. [c]CF_3CH_2OH was used as a reaction solvent. NaOTf was used as an additive.

their coupling constants in ^{1}H NMR spectrum (see Supporting Information). We demonstrated that direct and nonselective monofluorination of both compounds **2a** and **1a** worked by tuning the reactivity of the fluorinating reagents. The more reactive substrate **2a** required milder fluorinating reagent **6**, and less reactive substrate **1a** required more reactive **7**.

Compound **1g** was synthesized from **3a** because fluorinated intermediate **2g** was not observed and compound **2h** was isolated by the fluorination of compound **2a** (Scheme 1). Fluorination of **3a**[21] by LiHMDS and reagent **5** afforded compound **4g**, which was converted to **1g** in the following 2 steps.

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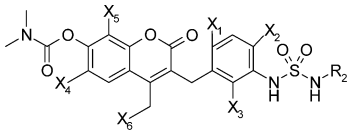
Table 1. Enzymatic and Celluar Activities and Pharmaceutical Properties of Monofluorinated Compounds



								IC$_{50}$ (nM)						
compd	X$_1$	X$_2$	X$_3$	X$_4$	X$_5$	X$_6$	R$_2$	HCT116	MEK1	C-Raf	solubility (μg/mL)	CL human (μL/min/mg)	PAMPA (10^{-6} cm/s)	AUC $_{po}$[a] (μM·h)
1a	H	H	H	H	H	H	H	95	230	530	32	6	6	104[c]
1b	F	H	H	H	H	H	H	950	940	830	9	6	5	176
1c	H	F	H	H	H	H	H	610	44	1100	37	6	6	ND
1d	H	H	F	H	H	H	H	18	53	13	273	6	6	40[b,c]
1e	H	H	H	F	H	H	H	87	110	180	114	6	5	61[b]
1f	H	H	H	H	F	H	H	140	240	120	ND	ND	ND	ND
1g	H	H	H	H	H	F	H	200	60	220	14	7	4	84
8a	H	H	H	H	H	H	Me	24	110	300	32	20	6	78[c]
8b	F	H	H	H	H	H	Me	550	2900	2400	51	22	5	75
8d	H	H	F	H	H	H	Me	9	38	8	81	13	5	70[c]
8e	H	H	H	F	H	H	Me	22	64	ND	55	13	5	99
8g	H	H	H	H	H	F	Me	30	66	120	72	22	4	86

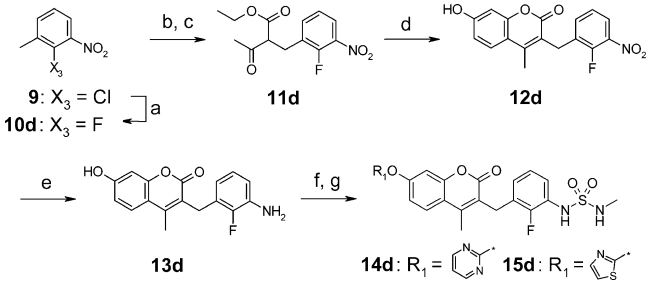
[a]Compounds were evaluated in 24 h exposure studies in mice at 100 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water. [b]At 50 mg/kg. [c]Sodium salt was used.

Among the six fluorinated positions, one position (X$_3$) contributed to stronger inhibitory activity on HCT116 cell growth and MEK/Raf in both the compounds (R$_2$ = H, Me) used to evaluate the fluorination effects (Table 1). For compounds **1d** and **8d** (X$_3$ = F), 3- to 5-fold enhancement of cell growth and MEK inhibitory activity and 40-fold enhancement of Raf inhibitory activity were observed. Three positions (X$_4$, X$_5$, and X$_6$) kept that level of activity after fluorination, and two positions (X$_1$ and X$_2$) resulted in decreased bioactivity.

Evaluation of water solubility, metabolic stability, and membrane permeability for the fluorinated compounds showed that all of these parameters were not significantly changed from our lead compound **1a** by monofluorination. Though the solubility of two compounds (**1b** and **1g**) was a third less than that of lead **1a**, the other seven derivatives kept or increased the solubility (four compounds had more than double the value). Because no specified fluorinated positions led to decreased water solubility (compounds **8b** and **8e** had comparable solubility to the parent **8a**), we concluded that monofluorinated compounds of our lead **1a** tend to keep their solubility at all positions. All of nine compounds kept the metabolic stability, as evaluated from human liver microsome. In spite of identifying oxidized metabolites at aromatic positions attached to sulfamide,[21] no clear improvement in microsomal stability was observed by fluorination at X$_1$, X$_2$, or X$_3$ (see below). Membrane permeability of all nine compounds, evaluated by PAMPA method, showed high enough and comparable values to our lead **1a**. AUCs after oral administration to mice were also similar to lead **1a**, the BA of which was 62%. By fluorine scanning of our lead **1a**, compounds for oral drugs with higher bioactivity, which retained their physicochemical properties, were identified.

For further derivatizations with fixed fluorine at X$_3$, a synthetic method available for large scale synthesis was established by modifying the reported procedures (Scheme 2).[21] The fluorine was introduced by substituting the chlorine with CsF to give compound **10d**. Bromination of benzyl

Scheme 2. Synthesis Suitable for Large Quantities[a]



[a]Reagents and conditions: (a) CsF (1.5 equiv), DMSO, 140 °C, 10 h, 82%; (b) NBS (1.2 equiv), benzoyl peroxide (0.1 equiv), CCl_4, reflux, 5 h; (c) NaH (1.0 equiv), ethyl acetoacetate (1.0 equiv), THF, 0 °C, 12 h, 42% (2 steps); (d) resorcinol (1.0 equiv), conc. H_2SO_4, 0 °C, 12 h, 64%; (e) $SnCl_2$ (5.0 equiv), EtOAc, reflux, 1.5 h, 71%; (f) 2-bromopyrimidine or 2-bromothiazole (4.0 equiv), Cs_2CO_3, DMF, 100 °C; (g) *N*-methyl-2-oxooxazolidine-3-sulfonamide (3.0 equiv), Et_3N (5.0 equiv), MeCN, 75 °C, 3.5 h.

position and the reaction with ethyl acetoacetate then afforded derivative **11d**. Converting to coumarin **12d** via Pechmann reaction with resorcinol, followed by reduction of a nitro group by $SnCl_2$, afforded aniline derivative **13d**. After introducing the pyrimidyl or thiazole group, sulfamide **14d** and **15d** were obtained by the reaction with *N*-methyl-2-oxooxazolidine-3-sulfonamide.

As shown in Table 2, over 10-fold increased inhibition of cell growth and Raf/MEK by fluorination at X$_3$ position was observed in the case of pyrimidyl and thiazole moieties at R$_1$. Again, solubility change by fluorination tended to be small: by half in the pyrimidine derivative and 1.5-fold in the thiazole derivative. Metabolic stability was improved in both compounds. Fluorination had the effect of blocking the aromatic ring hydrogen, potentially because carbamate, which was the major metabolic position, was substituted to more stable pyrimidine and thiazole moieties (see above). AUC values after

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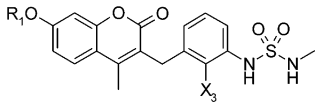
Table 2. Enzymatic and Celluar Activities and Pharmaceutical Properties of Monofluorinated Compounds 14 and 15



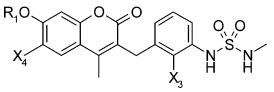
compd	R_1	X_3	IC_{50} (nM) HCT116	MEK1	C-Raf	solubility (μg/mL)	CL human (μL/min/mg)	PAMPA (10^{-6} cm/s)	AUC_{po}[a] (μM·h)
14a		H	190	810	>10000	29	20	6	223
14d		F	17	97	23	13	7	6	425
15a		H	160	59	1500	9	24	2	190[b]
15d		F	11	26	63	15	9	3	366[b]

[a]Compounds were evaluated in 24 h exposure studies in mice at 100 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water. [b]Sodium salt was used.

oral administration to mice increased 2-fold, reflecting an improved metabolic stability.

The positions X_3 and X_4, which were identified as keeping Raf/MEK inhibitory activity after fluorination, were further modified in the larger functional groups because they could be potential positions for enhancing bioactivity (Table 3). By

Table 3. Enzymatic and Celluar Activity and Pharmaceutical Properties of Coumarins Modified at X_3 or X_4



compd	R_1	X_3	X_4	IC_{50} (nM) HCT116	MEK1	C-Raf	solubility (μg/mL)	CL human (μL/min/mg)	AUC_{po}[a] (μM·h)
16		Me	H	330	4200	3600	<4	ND	ND
17		H	Cl	4	7	8	13	23	51[b]
18		H	I	8	5	25	8	33	16
19		H	Me	22	29	78	11	17	18
20		H	CCH	140	100	70	21	ND	ND
21		H	CN	24	85	55	40	15	39

[a]Compounds were evaluated in 24 h exposure studies in mice at 100 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water. [b]Sodium salt was used.

introducing a methyl group to X_3, the bioactivity was decreased (compound **16**). However, various modifications were acceptable at X_4 position (compounds **17**–**21**), and the strongest activity was obtained at a chlorine[21] or iodine. Fluorine scanning can also be utilized for identifying intensive modification positions because keeping bioactivity by fluorination may be a sign of vacant space existing between a drug and its target protein.[5] We noticed that all of the modifications in Table 3 resulted in decreased values for at least one of the physicochemical properties (solubility, metabolic stability, or permeability). Larger groups than fluorine resulted in negative factors for the physicochemical properties of our lead **1a**, proving the special nature of fluorine.

We identified compound **14d** as the best compound for further drug development. No strong CYP inhibition activity was observed in five different species, and the IC_{50} values tended to be decreased by fluorination (see Supporting Information). Inhibition of hERG at 10 μM was 25%, which was weak enough. The compound showed satisfactory PK data for mouse, rat, and monkey (Table 4) with good BA values

Table 4. PK Profile of Sodium Salt of 14d in Mouse, Rat, and Monkey[a]

parameter	mouse	rat	monkey
iv/po dose (mg/kg)	10/20	5.0/10	2.5/5.0
AUC_{inf} (μM·h), po	75	43	108
$t_{1/2}$ (h), iv	1.3	2.9	4.8
Cl (mL min^{-1} kg^{-1})	6.8	6.6	0.9
bioavailability (%)	75	84	59

[a]Vehicle: 5% DMSO/5% Cremophor EL/15% PEG400/15% HPCD/60% water.

(75%, 84%, and 59%, respectively) and good clearance values (6.8, 6.6, and 0.9 mL min^{-1} kg^{-1}, respectively). Potent antitumor effect was observed in the HCT116 xenograft model: ED_{50} of 1.4 mg/kg and TGI of 119% at 30 mg/kg (Figure 2). It showed no serious effect on body weight or any adverse clinical signs.

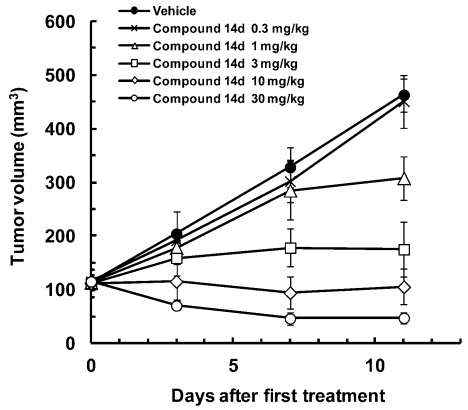


Figure 2. In vivo efficacy of sodium salt of **14d** in the HCT116 human colon cancer xenograft model. HCT116 cells were inoculated subcutaneously into the right flank of BALB-nu/nu mice. Tumors were allowed to establish growth after implantation before treatment was initiated. Pyrimidine derivative **14d** was administered orally once daily for 11 days, from day 0 to day 10. Tumor size was measured twice per week. Values are mean ± SD, n = 4.

Fluorine scanning by direct and nonselective monofluorination can be a powerful method of identifying compounds that have stronger efficacy than the parent compound while keeping the physicochemical properties. This ability to keep the physicochemical properties could be considered a particular advantage of a fluorinated compound, if changes of electronic structure by fluorination are limited, when compared with compounds introducing other moieties such as chlorine, iodine, methyl, etc. We demonstrated that the direct and nonselective monofluorination method could be superior to the normal hit-to-lead chemistry by stepwise synthesis because a single reaction afforded several derivatives, making it time- and cost-effective and also because utilizing both lead compound and key intermediates widened the possible choice of fluorination points.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental preparation of compounds, characterization, biological, in vitro physicochemical properties, and in vivo experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AUC, area under the curve; BA, bioavailability; CL, clearance; CYP, cytochrome P450; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; ED_{50}, median effective dose; ERK, extracellular signal-regulated kinase; hERG, human ether-a-go-go related gene; HMBC, heteronuclear multiple bond correlation spectroscopy; HPCD, 2-hydroxypropyl-β-cyclodextrin; HPLC, high performance liquid chlomatography; IC_{50}, half maximal inhibitory concentration; LiHMDS, lithium bis(trimethylsilyl)amide; MEK, mitogen-activated protein kinase kinase; NBS, *N*-bromosuccinimide; ND, no data; PAMPA, parallel artificial membrane permeability assay; PEG, polyethylene glycol; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, half-life period; Tf, trifluoromethanesulfonyl; TGI, tumor growth inhibition; THF, tetrahydrofuran; UV, ultraviolet

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(13) For examples, CLogP values of benzene (2.14) and F−Ph (2.29) are rather similar to each other than compared to other substitutions such as Cl−Ph (2.86), Br−Ph (3.01), I−Ph (3.27) and Me−Ph (2.64).

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