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Synthesis of indazole based diarylurea derivatives and their antiproliferative activity against tumor cell lines

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ABSTRACT

New series of indazole based diarylureas were synthesized and their anticancer activity against cancer cells H460, A549, OS-RC-2, HT-29, Lovo, HepG2, Bel-7402, SGC-7901 and MDA-MB-231 were examined. These derivatives of diarylureas, except azaindazole based diarylureas **5f**, 5l and **5m**, showed superior or similar activity against most of these selected cancer cell lines to the reference compound sorafenib. The effect of substituents on the indazole ring was also investigated. Derivatives with trifluoromenthy or halogen substituent on the indazole ring showed higher activity against the selected cancer cell lines than sorafenib. The acute toxicity assay showed that compounds **5a**, 5b and **5i** possessed lower toxicity than sorafenib. Compound **5i** with 4-(trifluoromenthy)-1*H*-indazole and 4-(trifluoromenthy) benzene moieties exhibited the most potent anticancer activity.

Cancer is a major public health problem in the world. The American Cancer Society estimates that one out of every four deaths in the United States is due to cancers.[1] Cancers of lung and bronchus, prostate, breast, colorectum, kidney and liver have been the most causes of cancer death.[1] Although the immense efforts of innumerable research have been made, the rates of cancer death are still in its high plateau.

The current treatments for cancers involve surgery, chemotherapy, radiotherapy, biological therapy (including immunotherapy and gene therapy), and various combinations.[2] Chemotherapies have been the backbone among these cancer treatments.[3] However, most of the current drugs are cytotoxic agents with the narrow therapeutic index and frequently acquired resistance.[3] The development of more effective and lower toxicity drugs is needed.

A considerable number and diversity of diarylureas have been identified as the promising, effective, and selective anti-cancer agents.[4–7] Sorafenib, for example, the first oral multi-kinase inhibitor, has shown good effects in renal cell carcinoma, hepatocellular carcinoma, non-small cell lung cancer and melanoma,[8–12] though concomitant toxicities[13–15] and drug resistance[16] cannot be ignored in clinic. Encouraged by these good effects of diarylurea derivatives, we designed a new series of diarylurea compounds containing indazole or azaindazole moiety based on the structural features of sorafenib (shown in Fig. 1 and Table 1). In this Letter, we show the synthesis of these new diarylurea derivatives and their activity against a series of human cancer cell lines including non-small cell lung cancer cells NCI-H460 and A549, colon cancer cells HT-29 and Lovo, hepatocellular carcinoma cells HepG2 and Bel-7402, renal cell carcinoma cells OS-RC-2, gastric carcinoma cells SGC-7901 and breast cancer cells MDA-MB-231.

The synthesis of this series diarylureas is shown in Scheme 1. In the presence of Cs_2CO_3, compound **3** was synthesized by reacting indazoles or azaindazoles with 4-fluoronitrobenzene in DMF. Compound **4** was achieved by reductive of compound **3** with $SnCl_2$ in concentrated hydrochloric acid. The desired compounds **5a**–**m** was obtained by slowly adding phenylisocyanate R^2 to the solution of compound **4** in CH_2Cl_2 under argon atmosphere. With this reaction route, 13 new indazole and azaindazole based diarylureas were obtained, and their chemical characteristics and analytic data are reported in Table 1.

The anticancer activity of these new diarylurea compounds in human cancer cell lines was evaluated by using the MTT assay.[17] The half-maximal inhibitory concentrations (IC_{50}s) were calculated and summarized in Table 2 with sorafenib as control drug.

Most of these compounds showed potent activity against one or more of these cell lines. As shown in Table 2, the IC_{50} of sorafenib against MDA-MB-231 was 2.0 μM, which is close to the published data of 2.6 μM.[18] The newly synthesized compound **5a** with 4-trifluoromenthy-1*H*-indazole moiety and compound **5b** containing 4-chloro-1*H*-indazole moiety showed similar or superior activity against MDA-MB-231 to sorafenib. Their IC_{50}s in MDA-MB-231 were 2.0 and 1.6 μM, respectively. These two compounds also showed similar or superior activity to sorafenib in NCI-H460, A549, HT-29, and Lovo cell lines. These results indicated that both trifluoromenthy and chloro-substituent at the 4 position of indazole

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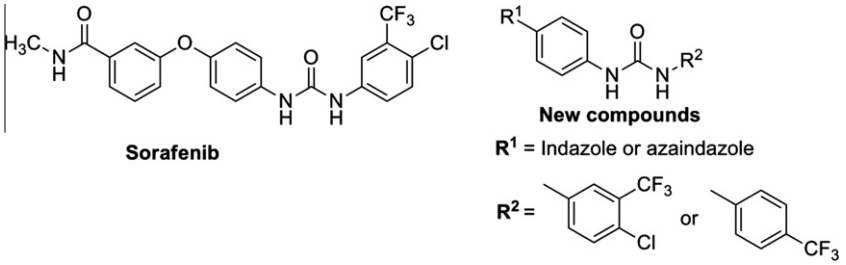
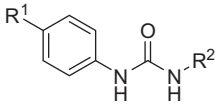


Figure 1. Chemical structures of sorafenib and indazole based diarylurea derivatives.

Table 1
Structures for desired compounds



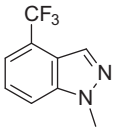
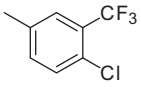
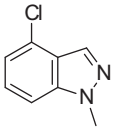
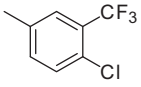
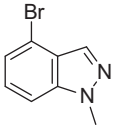
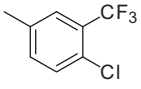
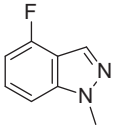
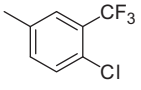
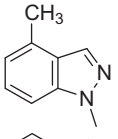
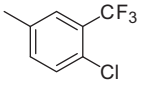
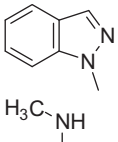
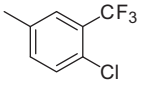
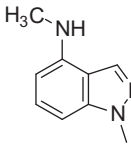
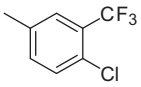
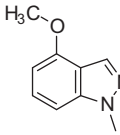
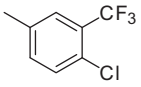
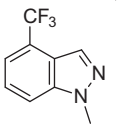
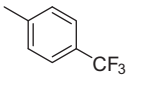
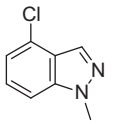
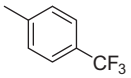
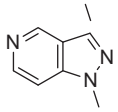
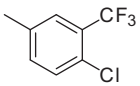
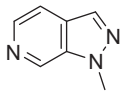
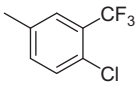
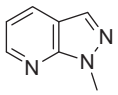
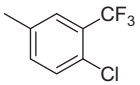
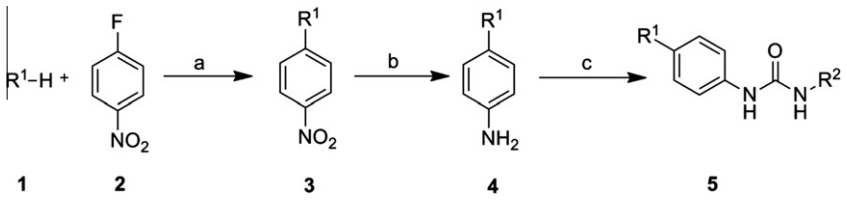
Compound no.	R^1	R^2	Analytic data
5a			HPLC (UV254): 99.6%, LC–MS ($C_{22}H_{13}ClF_6N_4O$, MW = 498): M+H = 499, M+Na = 521. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.47 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.68 (m, 3H), 8.04 (d, J = 9.0 Hz, 1H), 8.14 (m, 3H), 9.17 (s, 1H)
5b			HPLC (UV254): 98.5%, LC–MS ($C_{22}H_{13}Cl_2F_3N_4O$, MW = 464): M+H = 465, M+Na = 487. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 9.26 (s, 1H), 9.14 (s, 1H), 8.42 (s, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70 (m, 5H), 7.64 (d, J = 8.4 Hz, 1H), 7.48 (m, 1H), 7.35 (d, J = 7.2 Hz, 1H)
5c			HPLC (UV254): 99%. LC–MS ($C_{21}H_{13}BrClF_3N_4O$, MW = 508, 510): M+Na = 531, M+Na = 533. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.41 (t, J = 4.2 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.63–7.72 (m, 6H), 7.79 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 8.32 (d, J = 0.6 Hz, 1H), 9.13 (s, 1H), 9.25 (s,1H)
5d			HPLC (UV254): 99.8%, LC–MS ($C_{21}H_{13}ClF_4N_4O$, MW = 448): M+H = 449, M+Na = 471. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.06 (m, 1H), 7.49 (m, 1H), 7.62 (m, 2H), 7.70 (m, 5H), 8.14 (d, J = 2.4 Hz, 1H), 8.47 (s, 1H), 9.13 (s, 1H), 9.25 (s, 1H)
5e			HPLC (UV254): 100%, LC–MS ($C_{22}H_{16}ClF_3N_4O$, MW = 444): M+H = 44, M+Na = 467. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 2.60 (s, 3H), 7.04 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.68 (m, 5H), 8.14 (d, J = 2.4 Hz, 1H), 8.40 (s, 1H)
5f			HPLC (UV254): 99.7%, LC–MS ($C_{22}H_{14}ClF_3N_4O$, MW = 430): M+H = 431, M+Na = 453. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.27 (t, J = 7.5 Hz, 1H), 7.49 (m, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.69 (m, 4H), 7.79 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.35 (s, 1H)
5g			HPLC (UV254): 94.8 %, LC–MS ($C_{22}H_{17}ClF_3N_5O$, MW = 459): M+H = 459. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 2.86 (s, 3H), 6.12 (d, J = 7.8 Hz, 1H), 6.55 (s, 1H), 6.9 (d, J = 8.4 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.65 (m, 6H) , 8.14 (d, J = 2.4 Hz, 1H), 8.34 (s, 1H), 9.05 (s, 1H), 9.22 (s, 1H)
5h			HPLC (UV254): 100%, LC–MS ($C_{22}H_{16}ClF_3N_4O_2$, MW = 460): M+H = 461, M+Na = 483. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 3.97 (s, 3H), 6.71 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.4 (t, J = 16.2 Hz, 1H), 7.60–7.70 (m, 6H), 8.14 (d, J = 1.8 Hz, 1H), 8.28 (s, 1H), 9.08 (s, 1H), 9.23 (s, 1H)
5i			HPLC (UV254): 100%, LC–MS ($C_{22}H_{14}F_6N_4O$, MW = 464): M+H = 464, M+Na = 486. ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.47 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 9.0 Hz, 4H), 8.05 (d, J = 5.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 9.12 (s, 1H), 9.19 (s, 1H), 9.22 (s, 1H)

Table 1 (*continued*)

Compound no.	R^1	R^2	Analytic data
5j			HPLC (UV254): 99%, LC–MS ($C_{21}H_{14}ClF_3N_4O$, MW = 430): M+H = 431, M+Na = 453, ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 9.19 (s, 1H), 9.09 (s, 1H), 8.42 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (m, 8H), 7.48 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H)
5k			HPLC (UV254): 97.8%, LC–MS ($C_{20}H_{13}ClF_3N_5O$, MW = 431): M+H = 432, ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.67 (m, 6H), 7.78 (d, J = 6.0 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 8.47 (d, J = 6.0 Hz, 1H), 8.59 (s, 1H), 9.13 (s, 1H), 9.22 (s, 1H), 9.25 (s, 1H)
5l			HPLC (UV254): 100%. LC–MS ($C_{20}H_{13}ClF_3N_5O$, MW = 431): M+H = 432, ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.64 (d, J = 9.0 Hz, 1H), 7.68 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 7.69 (d, J = 2.4 Hz, 2H), 7.72 (d, J = 1.8 Hz, 2H), 7.90 (dd, J_1 = 1.2 Hz, J_2 = 5.4 Hz, 1H), 8.14 (d, J = 2.4 Hz, 1H), 8.37 (d, J = 5.4 Hz, 1H), 8.50 (s, 1H), 9.13 (s, 1H), 9.25 (s, 1H), 9.28 (s, 1H)
5m			HPLC (UV254): 100%. LC–MS ($C_{20}H_{13}ClF_3N_5O$, MW = 431): M+H = 432, M+Na = 454, ^{1}H NMR (600 MHz, DMSO-d_6) (ppm): δ 7.37 (dd, J_1 = 4.2 Hz, J_2 = 7.8 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 3H), 8.15 (dd, J_1 = 2.7 Hz, J_2 = 6.9 Hz, 3H), 8.38 (d, J = 1.8 Hz, 1H), 8.40 (s, 1H), 8.67 (dd, J_1 = 1.8 Hz, J_2 = 4.8 Hz, 1H), 9.05 (s, 1H), 9.22 (s, 1H)



Scheme 1. Synthesis of indazole based diarylurea derivatives. Reagents and conditions: (a) Cs_2CO_3, DMF; (b) $SnCl_2$, concentrated HCl, saturated $NaHCO_3$, pH 9, CH_2Cl_2, $MgSO_4$, silica gel column chromatography (eluent EtOAc/PE = 2:1); (c) CH_2Cl_2, Ar, 0 °C, methanol (yields: **5a**: 45%, **5b**: 33%, **5c**: 43%, **5d**: 36%, **5e**: 50%, **5f**: 49%, **5g**: 48%, **5h**: 52%, **5i**: 24%, **5j**: 80%, **5k**: 80%, **5l**: 81%, **5m**: 79%).

Table 2
IC_{50}s (μM) for desired compounds in nine human cancer cell lines after 72 h continuous exposure

NO.	NCI-H460	A549	OS-RC-2	HT-29	LOVO	HepG2	Bel-7402	SGC-7901	MDA-MB-231
5a	1.6	3	>32	2.9	3	8	16	>32	2
5b	1.3	3.1	3.1	4.6	3.6	1.9	2.5	4.6	1.6
5c	1.3	2.3	9.9	4	1.7	2.0	1.3	16.6	7.7
5d	3.4	3.8	32	8.2	9.8	29.5	16	32	3.1
5e	2.5	5.5	32	32	3.9	4	6.7	14.2	2.3
5f	5.5	9.9	32	18.2	8.7	8	10.6	>32	5
5g	2.6	4.9	10.6	5.9	6.3	3	5	6.9	3.6
5h	2.2	3.7	28.8	>32	>32	4	2.9	29.8	1.2
5i	0.8	0.8	4	3.3	2.2	1	1	4	2
5j	6.8	6	4.6	1	5.1	6.7	8	6	2.7
5k	1.4	3.4	>32	10.5	8	4	2.7	22.6	16
5l	4.8	10.6	>32	29.5	7.1	16	4	>32	>32
5m	16.6	>32	>32	>32	32	>32	20.9	>32	>32
Sorafenib	3.9	4	16	4	3.3	4	5.8	6.9	2

ring are favorable. This inference was supported by another halogen compound **5c** which has 4-bromo-1*H*-indazole moiety and also exhibited excellent inhibitory activity against NCI-H460, A549, HT-29, and Lovo cell lines. Notably, both compounds **5b** and **5c** showed stronger activity than sorafenib against hepatocellular carcinoma cell lines HepG2 and Bel-7402. The IC_{50}s in HepG2 and Bel-7402 were 1.9 and 2.0 μM for **5b** and 2.5 and 1.3 μM for **5c**, respectively. More encouragingly, compound **5b** showed very good activity against OS-RC-2 with IC_{50} at 3.1 μM and SGC-7901 with IC_{50} at 4.6 μM. In contrast, compounds **5d**, 5e or **5f**, with F-, Me-, or none-indazole substitute, respectively, showed less activity than compounds **5b** in most of these cell lines, which might be caused by their smaller atom space. However, compounds **5g** and **5h**, with MeN- and MeO-groups, exhibited similar or superior activity to sorafenib and compound **5b** against MDA-MB-231, NCI-H460, A549, HepG2, and Bel-7402 cell lines, which might be ascribed to their space effect and electric effect from MeN- or MeO- group.

All above eight diarylurea compounds have 4-chloro-3-(trifluoromenthy) benzene moiety as their R^2 (Table 1). By replacing this moiety with 4-(trifluoromenthy) benzene, two novel compounds **5i** and **5j** were synthesized (Table 1). Compound **5i** showed much more potential anticancer activity against all these cell lines, especially MDA-MB-231, NCI-H460, A549, HepG2, Bel-7402 and OS-RC-2, in which the IC_{50}s for compounds **5i** were 2.0, 0.8, 0.8, 1.0, 1.0 and 4.0 μM, respectively. The IC_{50}s of compound **5j** were similar to that of compounds **5a** and **5b** in most of the cell lines (Table 2).

To investigate the function of the indazole ring, three azaindazoles based diarylurea compounds **5k–m** were synthesized

(Table 1). Their IC_{50}s showed that all these three compounds have less activity in all these cell lines, indicating that the activity was diminished while the indazole ring was replaced by the azaindazole ring. These data suggested that the indazole ring is an important moiety for anticancer activity and the trifluoromenthy or halogen substituent at the 4 position of indazole ring is favorable.

We evaluated the acute toxicity for the representative compounds **5a**, 5b and **5i** in mice. The highest single oral dose of 2000 mg/kg for these compounds was tolerated without any sign of toxicity, while the tolerated single oral dose of sorafenib was 1460 mg/kg in mice. These results suggested that these new synthesized diarylurea compounds might have lower toxicity than sorafenib. Further toxicities of these compounds are currently underway.

In conclusion, a new series of indazole based diarylurea compounds were synthesized and their activity against human tumor cell lines was examined. Among them, compounds with trifluoromenthy and halogen substituents showed better effect than sorafenib. Compounds **5a**, 5b and **5i** were found to have lower toxicity than sorafenib. Compound **5i** could be developed as a promising agent for treatment of cancers.

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References and notes

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17. NCI-H460, A549, HT-29, Lovo, HepG2, Bel-7402, OS-RC-2, SGC-7901 and MDA-MB-231 cells were purchased from the American Type Cell Culture Collection (ATCC, USA) and maintained in RPMI-1640 or DMEM medium supplemented with 10% (v/v) heat-inactivated fetal bovine serum, penicillin–streptomycin (100 IU/mL–100 μg/mL), 2 mM glutamine, and 10 mM HEPES buffer at 37 °C in a humidified atmosphere (5% CO_2–95% air). Culture medium was changed every 2 days. Cells were harvested by brief incubation in 0.02% (w/v) trypsin in PBS (ICN, Aurora, USA), seeded in 96-well plates (3×10^3 per well) and then were incubated in humidified atmosphere for 24 h prior to exposure to various concentrations of test compounds for 72 h. Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay via adding 20 μL of MTT (5 mg/mL, Sigma, USA) and incubating for 4 h. The absorbance at 570 nm was measured on a microplate reader (Perkin-Elmer, USA), and the IC_{50}s were calculated.
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