Antifungal estrogen-like imidazoles. Synthesis and antifungal activities of thienyl and 1H-pyrrolyl derivatives of 1-aryl-2-(1H-imidazol-1-yl)ethane

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Preliminary communication

Antifungal estrogen-like imidazoles. Synthesis and antifungal activities of thienyl and 1*H*-pyrrolyl derivatives of 1-aryl-2-(1*H*-imidazol-1-yl)ethane

R Di Santo[1], R Costi[1], M Artico[1]*, S Massa[2], C Musiu[3], F Scintu[3], M Putzolu[3], P La Colla[3]

[1]*Dipartimento di Studi Farmaceutici, Università di Roma 'La Sapienza', P le Aldo Moro 5, 00185 Rome;*
[2]*Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, 53100 Siena;*
[3]*Dipartimento di Biologia Sperimentale, Università di Cagliari, V le Regina Margherita 45, 09124 Cagliari, Italy*

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Summary — Reaction of arylacetyl chlorides on thiophene or pyrrole derivatives furnished 2-aryl-1-(2-thienyl)- or 2-aryl-1-(1*H*-pyrrol-2-yl)-1-ethanones. Reduction of ketones to the corresponding carbinols and reaction of the latter compounds with 1,1'-sulfonyldiimidazole or 1,1'-carbonyldiimidazole gave 2-thienyl- and 1*H*-pyrrol-2-yl-1-aryl-2-(1*H*-imidazol-1-yl)ethanes, respectively. The new compounds were tested in vitro against a variety of pathogenic fungi in comparison with miconazole and bifonazole. Some 5-chloro-2-thienyl derivatives were endowed with good antifungal activity, particularly against *Candida albicans* and *Cryptococcus neoformans*.

azole / antifungal agent / 1,2-diarylethaneimidazole

Introduction

In a previous work [1, 2] we hypothesized that imidazoles incorporating a 1,2-diarylethane moiety would affect enzymes involved in the biosynthesis of fungal membrane steroids such as lanosterol **1** and ergosterol, because of their resemblance to the structure of diethylstilbestrole **2**, a non-steroidal hormone with estrogen activity. As a consequence of this interference, 1-(1*H*-imidazol-1-yl)-1,2-diarylethane derivatives have been supposed to exert an inhibitory activity against human pathogenic fungi.

Synthetic efforts in this direction and subsequent antifungal assays have confirmed our hypothesis and the modification of some structural features of the above compounds has led to products with enhanced activity. This new class of antifungal imidazoles, called 'estrogen-like imidazoles' **3**, has been further investigated and new synthetic and microbiological studies have led to the identification of two derivatives, namely 1-(1*H*-imidazol-1-yl)-1-(4-methoxyphenyl)-2-(2,4-dichlorophenyl)ethane **4** and 1-(1*H*-imidazol-1-yl)-1-(4-methoxyphenyl)-2-(4-aminophenyl)ethane **5**, which we have shown to be endowed with antifungal activity comparable to that of miconazole, bifonazole and ketoconazole [3].

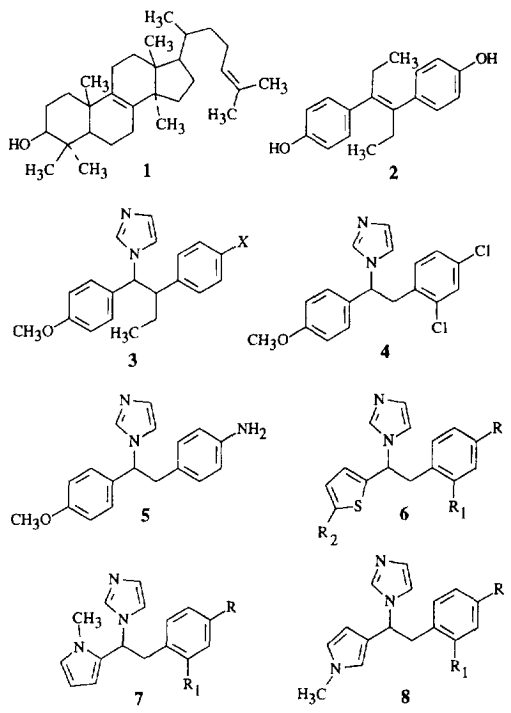
*Correspondence and reprints

With the aim of more deeply investigating the SAR of this new class of antifungal agents, we explored the influence exerted on the antifungal activity by the replacement of benzene with heterocyclic rings such as thiophene and pyrrole. Therefore, we synthesized derivatives **6–8** (scheme 1) and tested them against a range of human pathogenic fungi.

The new compounds were tested in vitro against a variety of pathogenic fungi such as *Candida albicans*, *Candida tropicalis*, *Candida paratropicalis*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Microspora canis* and *Trychophyton mentagrophytes*, together with two imidazole antifungal agents, miconazole [4] and bifonazole [5], used as reference drugs.

Chemistry

Friedel–Crafts reaction between phenacyl chlorides and thiophene derivatives in the presence of aluminium trichloride afforded 2-aryl-1-(2-thienyl)-1-ethanones **9**, which were reduced to the corresponding carbinols **10** by treatment with $LiAlH_4$. Reaction of **10** with 1,1'-sulfonyl diimidazole afforded the required imidazoles **6** (scheme 2). Arylacylation of 1-methylpyrrole afforded 2-arylacetyl (**11**) and 3-arylacetyl (**12**) isomers, which in turn were reduced with $NaBH_4$ to carbinols **13** and **14**, respectively. These derivatives were then transformed into the related imidazoles **7**



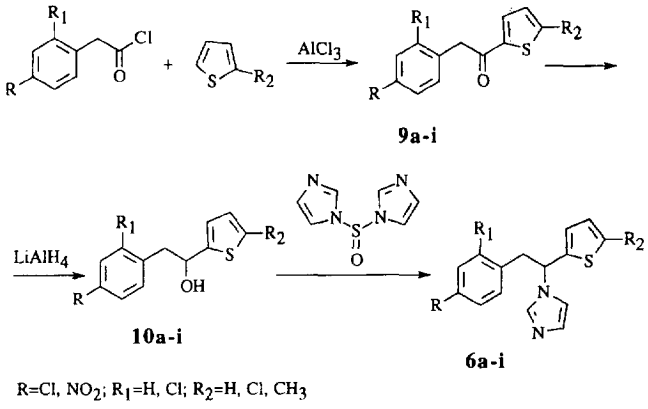
Scheme 1.

and **8** by reaction with 1,1'-carbonyldiimidazole (CDI) (scheme 3). Amino derivatives **6j,k,l**, **7d** and **8d** were obtained by reduction of the corresponding nitro derivatives **6c,f,i**, **7c** and **8c** with $SnCl_2 \cdot 2H_2O$ in concentrated hydrochloric acid (scheme 4). Chemical and physical data for derivatives **6–14** are reported in table I.

Microbiological results and discussion

The results of the in vitro cytotoxicity and antifungal assays of thienyl (**6a–l**) and 1*H*-pyrrolyl (**7a–d** and **8a–d**) derivatives of 1-aryl-2-(1*H*-imidazol-1-yl)-ethane are reported in table II. In general, when tested against the CD4+ T-cell line, the new imidazoles showed the same degree of cytotoxicity of the reference drugs.

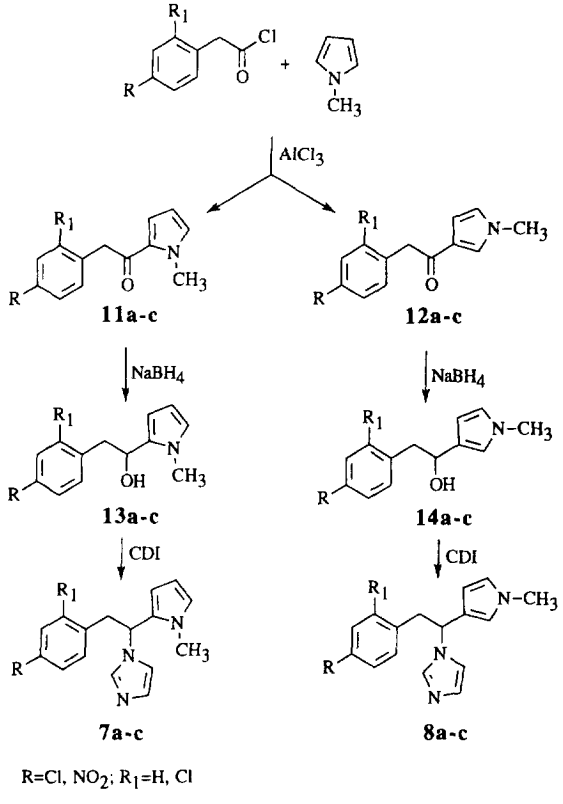
Pyrrolyl derivatives, either 1*H*-pyrrol-2-yl or 1*H*-pyrrol-3-yl, resulted inactive against all the pathogenic fungi tested. Therefore, the replacement of the aryl moiety of derivatives **4** and **5** with a pyrrole ring clearly results in a dramatic decrease of antifungal activity. A similar behaviour was also observed



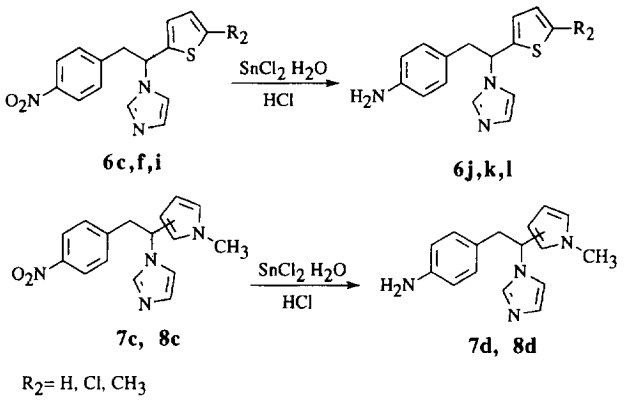
Scheme 2.

when the aryl portion was replaced by the thiophene ring, although some activity was obtained with 5-substituted thiophenes.

The introduction of a chlorine atom or a methyl group at position 5 of the 2-thienyl moiety led to



Scheme 3.



Scheme 4.

derivatives with selective activity against *Candida* spp (*C albicans*, *C tropicalis* and *C paratropicalis*) and *C neoformans*, but with no activity against *A fumigatus*, *M canis* and *T mentagrophytes* at concentrations below the CC_{50}.

Among the 5-chloro-2-thienyl imidazoles, the best activities were obtained when two chlorine atoms (compound **6e**) or an amino group (compound **6k**) were introduced in the phenyl ring. Against *C albicans* and *C paratropicalis* compound **6e** was as active as bifonazole and five times less active than miconazole. On the other hand, compound **6k** was 1.5 times more active than bifonazole and only two times less active than miconazole.

With the sole exception of the aminoaryl derivatives (**6k** and **6l**), the chlorothiophene and methylthiophene derivatives were all active against *C neoformans*, with potencies comparable to those exhibited by miconazole and bifonazole.

In conclusion, when compared to previously reported diarylethane imidazoles **4** and **5**, the replacement of the chloroaryl moiety with the bioisostere chlorothienyl in the diarylethane estrogen-like pharmacophore, although retaining some antifungal activity, does not ameliorate the potency.

As observed in previous studies [1, 3], the 2,4-dichloro and 4-amino substituents in the phenyl ring is determinant for antifungal activity. With chlorine as substituent, the best activity was obtained in the presence of three chlorine atoms; in fact, **6e** was by far more active than the dichloro derivative **6d**. Moreover, the importance of the 4-aminophenyl moiety as a pharmacophore was confirmed by the present study and allows us to conclude that the 2,4-dichorophenyl and 4-aminophenyl moieties can be claimed as bioisosteres.

Differently from miconazole and bifonazole, our derivatives are selectively active against *Candida* and *Cryptococcus*, but are totally inactive against the other fungal species tested (*A fumigatus*, *M canis* and *T mentagrophytes*).

Experimental protocols

Chemistry

Melting points were determined on an Electrothermal IA6304 apparatus and are uncorrected. Infrared spectra (Nujol mulls) were run on a Perkin Elmer 1310 spectrophotometer. ^{1}H-NMR spectra (table III) were recorded with a Varian Gemini 200 (200 MHz) using $CDCl_3$ as solvent, except for **6j**, **6l**, **7d**, **8d** which were performed in DMSO-d_6. Column chromatography purifications were performed on silica gel Merck (70-230 Mesh) and alumina Merck (70-230 Mesh). Stratocrom SIF Carlo Erba (silica-gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator) were employed for TLC. Elemental analyses were performed by Analytical Laboratories of Dipartimento di Scienze Farmaceutiche, University of Padova (Italy); analytical results were within ±0.4% of theoretical values. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvents after reactions and extractions involved the use of a rotatory evaporator (Büchi) operating at reduced pressure (approximately 20 bar).

2-Aryl-1-(2-thienyl)ethanones ***9a–i***

Aluminium trichloride (7.87 g, 59 mmol) was added in small portions over 30 min to a well-stirred solution of thiophene derivative (thiophene, 2-chlorothiophene or 2-methylthiophene) (118 mmol) and arylacetylchloride (59 mmol) in methylene chloride (100 mL) cooled and stirred at 0 °C (for reaction conditions see table I). Treatment with crushed ice (500 g) and concentrated hydrochloric acid (22 mL), followed by extraction with ethyl acetate (3 x 150 mL), furnished a solution which was washed with brine (3 x 300 mL), then with a saturated solution of sodium hydrogen carbonate (3 x 300 mL), again with brine (3 x 300 mL) and then dried. Removal of solvent afforded crude **9a–i** which were purified on a silica-gel column (alumina for **9c,f,i**) using chloroform as an eluent.

Arylpyrrolylethanones ***11a–c*** *and* ***12a–c***

Aluminium trichloride (8.27 g, 62 mmol) was added in small portions over 30 min to a well-stirred solution of 1-methylpyrrole (9.98 g, 123 mmol) and arylacetylchloride (59 mmol) in methylene chloride (100 mL) cooled at –20 °C. After stirring at –20 °C (for reaction times see table I) the mixture was treated with crushed ice (500 g) and concentrated hydrochloric acid (22 mL) and then extracted with ethyl acetate (3 x 150 mL). The organic solution was washed with brine (3 x 300 mL), then with a saturated solution of sodium hydrogen carbonate (3 x 300 mL), with brine again (3 x 300 mL) and then dried. Removal of solvent afforded a mixture of ethanones **11a–c** and **12a–c**, which were separated by chromatography on a silica-gel column (alumina for **11c** and **12c**) (chloroform as eluent). Elution furnished firstly 2-aryl-1-(1-methyl-1*H*-pyrrol-2-yl)-ethanones **11a–c** and then 2-aryl-1-(1-methyl-1*H*-pyrrol-3-yl)-ethanones **12a–c**.

2-Aryl-1-(2-thienyl)ethanols ***10a–i***

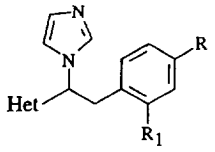
A solution of ethanone **9a–i** (12 mmol) in anhydrous tetrahydrofuran (75 mL) was added to a well-stirred suspension of lithium aluminium hydride (610 mg, 16 mmol) in the same

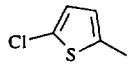
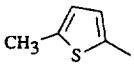
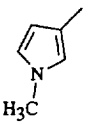
Table I. Chemical and physical data of derivatives **6–14**.

Compound	*R*	R_1	R_2	*Fomula*	*Molecular weight*	*Mp (°C)*	*Recrystallization*[a] *solvent*	*Yield (%)*	*Reaction time*	*Analysis*
6a	Cl	H	H	$C_{15}H_{13}ClN_2S$	288.79	134–135[b]	A[b]	47	4 h	C, H, N, Cl, S[c]
6b	Cl	Cl	H	$C_{15}H_{12}Cl_2N_2S$	323.24	149–150[b]	B[b]	59	7.5 h	C, H, N, Cl, S[c]
6c	NO_2	H	H	$C_{15}H_{13}N_3O_2S$	299.35	169–171[b]	B[b]	27	2 h	C, H, N, S[c]
6d	Cl	H	Cl	$C_{15}H_{12}Cl_2N_2S$	323.24	109–110[b]	C[b]	34	7.5 h	C, H, N, Cl, S[c]
6e	Cl	Cl	Cl	$C_{15}H_{11}Cl_3N_2S$	357.68	109–111[b]	D[b]	24	7.5 h	C, H, N, Cl, S[c]
6f	NO_2	H	Cl	$C_{15}H_{12}ClN_3O_2S$	333.79	63–65	E	45	3.5 h	C, H, N, Cl, S
6g	Cl	H	CH_3	$C_{16}H_{15}ClN_2S$	302.82	130–131[b]	C[b]	57	2 h	C, H, N, Cl, S[c]
6h	Cl	Cl	CH_3	$C_{16}H_{14}Cl_2N_2S$	337.27	143–144[b]	F[b]	56	2 h	C, H, N, Cl, S[c]
6i	NO_2	H	CH_3	$C_{16}H_{15}N_3O_2S$	313.37	148–150[b]	A[b]	57	1.5 h	C, H, N, S[c]
6j	NH_2	H	H	$C_{15}H_{15}N_3S$	269.36	170–171[b]	B[b]	79	4 h	C, H, N, S[c]
6k	NH_2	H	Cl	$C_{15}H_{14}ClN_3S$	303.81	111–113[b]	C[b]	62	4 h	C, H, N, Cl, S[c]
6l	NH_2	H	CH_3	$C_{16}H_{17}N_3S$	283.39	114–115[b]	A[b]	69	5.5 h	C, H, N, S[c]
7a	Cl	H	–	$C_{16}H_{16}ClN_3$	285.78	132–134	E	82	1.5 h	C, H, N, Cl
7b	Cl	Cl	–	$C_{16}H_{15}Cl_2N_3$	320.22	136–137	E	60	2 h	C, H, N, Cl
7c	NO_2	H	–	$C_{16}H_{16}N_4O_2$	296.33	166–167	G	70	1.5 h	C, H, N
7d	NH_2	H	–	$C_{16}H_{18}N_4$	266.35	82–84[b]	A[b]	48	5.5 h	C, H, N[c]
8a	Cl	H	–	$C_{16}H_{16}ClN_3$	285.78	102–104	E	10	1.5 h	C, H, N, Cl
8b	Cl	Cl	–	$C_{16}H_{15}Cl_2N_3$	320.22	98–99	E	43	3 h	C, H, N, Cl
8c	NO_2	H	–	$C_{16}H_{16}N_4O_2$	296.33	135–137	E	45	3 h	C, H, N
8d	NH_2	H	–	$C_{16}H_{18}N_4$	266.35	101–102[b]	A[b]	51	5 h	C, H, N[c]
9a	Cl	H	H	$C_{12}H_9ClOS$	236.72	97–98	H	84	1 h	C, H, Cl, S
9b	Cl	Cl	H	$C_{12}H_8Cl_2OS$	271.16	68–70	H	66	40 min	C, H, Cl, S
9c	NO_2	H	H	$C_{12}H_9NO_3S$	247.27	131–132	E	47	25 min	C, H, N, S
9d	Cl	H	Cl	$C_{12}H_8Cl_2OS$	271.16	94–95	H	91	25 min	C, H, Cl, S
9e	Cl	Cl	Cl	$C_{12}H_7Cl_3OS$	305.61	100–101	H	91	1 h	C, H, Cl, S
9f	NO_2	H	Cl	$C_{12}H_8ClNO_3S$	281.71	78–79	E	65	20 min	C, H, N, Cl, S
9g	Cl	H	CH_3	$C_{13}H_{11}ClOS$	250.74	90–91	H	37	1 h	C, H, Cl, S
9h	Cl	Cl	CH_3	$C_{13}H_{10}Cl_2OS$	285.19	115–116	H	20	35 min	C, H, Cl, S
9i	NO_2	H	CH_3	$C_{13}H_{11}NO_3S$	261.30	105–107	E	17	20 min	C, H, N, S
10a	Cl	H	H	$C_{12}H_{11}ClOS$	238.73	Oil	–	96	5.5 h	C, H, Cl, S[c]
10b	Cl	Cl	H	$C_{12}H_{10}Cl_2OS$	273.18	84–85	I	81	3.5 h	C, H, Cl, S
10c	NO_2	H	H	$C_{12}H_{11}NO_3S$	249.28	84–86	E	100	15 min	C, H, N, S
10d	Cl	H	Cl	$C_{12}H_{10}Cl_2OS$	273.18	Oil	–	100	1.5 h	C, H, Cl, S[c]
10e	Cl	Cl	Cl	$C_{12}H_9Cl_3OS$	307.62	Oil	–	99	2 h	C, H, Cl, S[c]
10f	NO_2	H	Cl	$C_{12}H_{10}ClNO_3S$	283.73	69–71	E	100	10 min	C, H, N, Cl, S
10g	Cl	H	CH_3	$C_{13}H_{13}ClOS$	252.76	Oil	–	81	1.5 h	C, H, Cl, S[c]
10h	Cl	Cl	CH_3	$C_{13}H_{12}Cl_2OS$	287.20	Oil	–	100	1.5 h	C, H, Cl, S[c]
10i	NO_2	H	CH_3	$C_{13}H_{13}NO_3S$	263.31	86–88	E	93	15 min	C, H, N, S
11a	Cl	H	–	$C_{13}H_{12}ClNO$	233.70	Oil	–	50	20 min	C, H, N, Cl[c]
11b	Cl	Cl	–	$C_{13}H_{11}Cl_2NO$	268.14	111–113	I	60	40 min	C, H, N, Cl
11c	NO_2	H	–	$C_{13}H_{12}N_2O_3$	244.25	111–112	E	25	20 min	C, H, N
12a	Cl	H	–	$C_{13}H_{12}ClNO$	233.70	114–116	E	14	20 min	C, H, N, Cl
12b	Cl	Cl	–	$C_{13}H_{11}Cl_2NO$	268.14	109–110	H	31	40 min	C, H, N, Cl
12c	NO_2	H	–	$C_{13}H_{12}N_2O_3$	244.25	140–142	E	8	20 min	C, H, N
13a	Cl	H	–	$C_{13}H_{14}ClNO$	235.71	54-56	H	100	15 h	C, H, N, Cl
13b	Cl	Cl	–	$C_{13}H_{13}Cl_2NO$	270.16	74–76	I	99	1.5 h	C, H, N, Cl
13c	NO_2	H	–	$C_{13}H_{14}N_2O_3$	246.27	65–66	E	92	7 h	C, H, N
14a	Cl	H	–	$C_{13}H_{14}ClNO$	235.71	68–69	J	96	6 h	C, H, N, Cl
14b	Cl	Cl	–	$C_{13}H_{13}Cl_2NO$	270.16	72–74	H	74	7 h	C, H, N, Cl
14c	NO_2	H	–	$C_{13}H_{14}N_2O_3$	246.27	99–101	E	100	2.5 h	C, H, N

[a]A: absolute ethanol/ethyl ether; B: absolute ethanol; C: isopropyl alcohol/isopropyl ether; D: ethyl acetate; E: benzene/cyclohexane; F: isopropyl alcohol; G: benzene; H: cyclohexane; I: *n*-hexane; J: cyclohexane/*n*-hexane. [b]These data refer to the nitrate salt. [c]Microanalysis performed on chromatographically pure product.

Table II. Antifungal activities of imidazoles **6–8**.



Compound	*Het*	*CC_{50}*[b]	*R*	*R_1*	*MIC (μM)*[a]						
					C albicans	*C paratropicalis*	*C tropicalis*	*C neoformans*	*A fumigatus*	*M canis*	*T mentagrophytes*
6a		44	Cl	H	75	150	75	19	150	>300	75
6b		37	Cl	Cl	>37	>37	>37	4.7	>37	>37	19
6c		59	NO_2	H	150	300	300	37.5	>300	>300	>300
6j		24	NH_2	H	300	>300	>300	300	>300	150	>300
6d		37.5	Cl	H	37.5	37.5	37.5	1.2	>37.5	>37.5	>37.5
6e		29	Cl	Cl	18	18	19	1.2	>29	>29	>29
6f		35	NO_2	H	75	75	75	4.7	>35	>35	>35
6k		4.4	NH_2	H	9.4	9.4	18.7	37.5	>300	150	37.5
6g		18	Cl	H	>18	>18	>18	4.7	>18	>18	>18
6h		22	Cl	Cl	19	>22	>22	4.7	>22	>22	>22
6i		34	NO_2	H	150	150	150	9.4	>300	>300	>300
6l		9	NH_2	H	37.5	37.5	75	37.5	>300	300	75
7a		>200	Cl	H	>300	>300	>300	150	>300	>300	150
7b		41	Cl	Cl	>300	>300	>300	75	>300	>300	150
7c		206	NO_2	H	>300	>300	>300	300	>300	>300	>300
7d		23.6	NH_2	H	>300	>300	>300	>300	>300	>300	>300
8a		58.6	Cl	H	>300	>300	>300	75	>300	>300	300
8b			Cl	Cl	>300	150	300	37.5	300	>300	37.5
8c			NO_2	H	>300	>300	>300	150	>300	>300	300
8d			NH_2	H	>300	>300	>300	300	>300	>300	>300
Miconazole		18	–	–	3.7	3.7	0.9	0.9	1.9	1.9	0.9
Bifonazole		28	–	–	15	15	30	3.7	3.7	3.7	3.7

[a]Minimum inhibitory concentration: the lowest concentration that inhibits the test microorganism. [b]Cytotoxic concentration (μM) of compound required to reduce the viability of mock-infected MT-4 cells by 50%.

solvent (75 mL) cooled to 0 °C. The mixture was stirred at room temperature (see table I) and then carefully treated with crushed ice. The inorganic precipitate was removed and the solution was concentrated and shaken with ethyl acetate (3 x 150 mL). The organic extracts were collected, washed with brine (3 x 300 mL), dried and evaporated. Crude **10a–i** were used for the next reaction without further purification.

*Arylpyrrolylethanols **13a–c** and **14a–c***
Ethanone **11a–c** or **12a–c** (25 mmol) was dissolved in tetrahydrofuran 50 mL and water (1.6 mL) and treated with sodium borohydride (4.69 g, 124 mmol). The mixture was refluxed (see table I), then cooled and evaporated. The residue was treated with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine (3 x 100 mL) and dried. After removal of solvent pure ethanols **13a–c** and **14a–c** were obtained.

*2-Aryl-1-(1H-imidazol-1-yl)-1-(2-thienyl)ethanes **6a–i***
Thionyl chloride (3.0 mL, 4.9 g, 41 mmol) was dropped onto an ice-cooled solution of 1*H*-imidazole (11.17 g, 164 mmol) in anhydrous acetonitrile (70 mL). The mixture was stirred at 0 °C for 1 h, then filtered. The organic solution was added onto a solution of alcohol **10a–i** (10 mmol) in anhydrous acetonitrile (40 mL). The mixture was stirred at room temperature (see table I), then was concentrated and the residue was dissolved in ethyl acetate (150 mL). The organic solution was washed with brine (3 x 100 mL), dried and evaporated. The residue was chromatographed on alumina column (ethyl acetate as eluent) to yield pure **6a–i**.

*Arylimidazolylpyrrolylethanes **7a–c** and **8a–c***
A solution of alcohol **13a–c** or **14a–c** (12 mmol) and 1,1'-carbonyl diimidazole (8.4 g, 52 mmol) in anhydrous acetonitrile (150 mL) was stirred at room temperature (see table I).

Table III. ^{1}H-NMR data for compounds **6–8**.

Compound	*δ (ppm)*
6a	3.23–3.48 (m, 2H, CH_2), 5.42 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.8 Hz, CH), 6.78–7.24 (m, 10H, thiophene, imidazole and benzene H)
6b	3.43 (dd, 1H, J_1 = 13.8 Hz, J_2 = 9.8 Hz, CH_2), 3.74 (dd, 1H, J_1 = 13.8 Hz, J_3 = 5.2 Hz, CH_2), 5.69 (dd, 1H, J_2 = 9.8 Hz, J_3 = 5.2 Hz, CH), 6.73–7.40 (m, 9H, thiophene, imidazole and benzene H)
6c	3.49–3.71 (m, 2H, CH_2), 5.59 (dd, 1H, J_1 = 9.1 Hz, J_2 = 6.2 Hz, CH), 6.96–7.58 (m, 8H, thiophene, imidazole and benzene H near CH_2), 8.09–8.14 (m, 2H, benzene H near NO_2)
6d	3.27–3.49 (m, 2H, CH_2), 5.39 (dd, 1H, J_1 = 9.0 Hz, J_2 = 6.0 Hz, CH), 6.70–7.34 (m, 9H, thiophene, imidazole and benzene H)
6e	3.36 (dd, 1H, J_1 = 15.0 Hz, J_2 = 9.6 Hz, CH_2), 3.64 (dd, 1H, J_1 = 15.0 Hz, J_3 = 5.6 Hz, CH_2), 5.56 (dd, 1H, J_2 = 9.6 Hz, J_3 = 5.6 Hz, CH), 6.68–7.40 (m, 8H, thiophene, imidazole and benzene H)
6f	3.44–3.66 (m, 2H, CH_2), 5.49 (dd, 1H, J_1 = 9.0 Hz, J_2 = 6.1 Hz, CH), 6.75–7.37 (m, 7H, thiophene, imidazole and benzene H near CH_2), 8.08–8.13 (m, 2H, benzene H near NO_2)
6g	2.45 (s, 3H, CH_3), 3.27–3.52 (m, 2H, CH_2), 5.40 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.8 Hz, CH), 6.59–7.33 (m, 9H, thiophene, imidazole and benzene H)
6h	2.45 (s, 3H, CH_3), 3.38 (dd, 1H, J_1 = 13.7 Hz, J_2 = 9.8 Hz, CH_2), 3.66 (dd, 1H, J_1 = 13.7 Hz, J_3 = 5.2 Hz, CH_2), 5.59 (dd, 1H, J_2 = 9.8 Hz, J_3 = 5.2 Hz, CH), 6.63–7.49 (m, 8H thiophene, imidazole and benzene H)
6i	2.44 (s, 3H, CH_3), 3.40–3.65 (m, 2H, CH_2), 5.48 (dd, 1H, J_1 = 9.8 Hz, J_2 = 5.2 Hz, CH), 6.55–7.34 (m, 7H, thiophene, imidazole and benzene H near CH_2), 8.05–8.09 (m, 2H, benzene H near NO_2)
6j	3.30 (m, 2H, CH_2), 5.10 (bs, 2H, NH_2), 5.78 (m, 1H, CH), 6.36 (m, 2H, benzene H near NH_2), 6.75–7.67 (m, 8H, thiophene, imidazole and benzene H near CH_2)
6k	2.61 (bs, 2H, NH_2), 3.16–3.39 (m, 2H, CH_2), 5.33 (dd, 1H, J_1 = 8.9 Hz, J_2 = 6.0 Hz, CH), 6.50–7.34 (m, 9H, thiophene, imidazole and benzene H)
6l	2.35 (s, 3H, CH_3), 3.25 (m, 2H, CH_2), 4.95 (bs, 2H, NH_2), 5.67 (m, 1H, CH), 6.33–7.41 (m, 9H, thiophene, imidazole and benzene H)
7a	3.19–3.32 (m, 4H, overlapped CH_3 and 1H CH_2), 3.52 (dd, 1H, J_1 = 13.7 Hz, J_2 = 4.3 Hz, CH_2), 5.21 (dd, 1H, J_2 = 4.3 Hz, J_3 = 10.2 Hz, CH), 6.15 (m, 1H, pyrrole β-H), 6.42–7.26 (m, 9H, pyrrole, imidazole and benzene H)
7b	3.25–3.37 (m, 4H, overlapped CH_3 and 1H CH_2), 3.72 (dd, 1H, J_1 = 13.7 Hz, J_2 = 4.7 Hz, CH_2), 5.42 (dd, 1H, J_2 = 4.7 Hz, J_3 = 10.2 Hz, CH), 6.16 (m, 1H, pyrrole β-H), 6.45–7.40 (m, 8H, pyrrole, imidazole and benzene H)
7c	3.28 (s, 3H, CH_3), 3.44 (dd, 1H, J_1 = 13.5 Hz, J_2 = 10.4 Hz, CH_2), 3.67 (dd, 1H, J_1 = 13.5 Hz, J_3 = 4.3 Hz, CH_2), 5.31 (dd, 1H, J_2 = 10.4 Hz, J_3 = 4.3 Hz, CH), 6.17 (m, 1H, pyrrole β-H), 6.45–7.37 (m, 7H, pyrrole, imidazole and benzene H near CH_2), 8.09–8.13 (m, 2H, benzene H near NO_2)
7d	3.12–3.35 (m, 5H, overlapped CH_3 and CH_2), 4.87 (bs, 2H, NH_2), 5.48 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.9 Hz, CH), 5.95 (m, 1H, pyrrole β-H), 6.31–7.45 (m, 9H, pyrrole, imidazole and benzene H)
8a	3.15–3.43 (m, 2H, CH_2), 3.61 (s, 3H, CH_3), 5.21 (dd, 1H, J_1 = 9.5 Hz, J_2 = 5.4 Hz, CH), 6.04 (m, 1H, pyrrole β-H), 6.34–7.35 (m, 9H, pyrrole, imidazole and benzene H)
8b	3.26 (dd, 1H, J_1 = 13.8 Hz, J_2 = 9.8 Hz, CH_2), 3.54–3.62 (m, 4H, overlapped CH_3 and 1H CH_2), 5.37 (dd, 1H, J_2 = 9.8 Hz, J_3 = 5.1 Hz, CH), 6.09 (m, 1H, pyrrole β-H), 6.51–7.37 (m, 8H, pyrrole, imidazole and benzene H)
8c	3.31–3.58 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 5.29 (dd, 1H, J_1 = 9.2 Hz, J_2 = 5.7 Hz, CH), 6.06 (m, 1H, pyrrole β-H), 6.50–7.36 (m, 7H, pyrrole, imidazole and benzene H near CH_2), 8.04–8.10 (m, 2H, benzene H near NO_2)
8d	3.09–3.19 (m, 2H, CH_2), 3.52 (s, 3H, CH_3), 4.79 (bs, 2H, NH_2), 5.25 (m, 1H, CH), 5.99 (m, 1H, pyrrole β-H), 6.33–7.45 (m, 9H, pyrrole, imidazole and benzene H)

The solvent was removed and the residue was dissolved in ethyl acetate (300 mL). The organic solution was washed with brine (3 x 200 mL) and dried. Evaporation of the solvent afforded imidazole derivatives **7a–c** and **8a–c**, which were purified on alumina column (ethyl acetate as eluent).

*2-(4-Aminophenyl)-1-(1H-imidazol-1-yl)-1-(2-thienyl)ethanes **6j,k,l**, 2-(4-aminophenyl)-1-(1H-imidazol-1-yl)-1-(1-methyl-1H-pyrrol-2-yl)ethane **7d** and 2-(4-aminophenyl)-1-(1H-imidazol-1-yl)-1-(1-methyl-1H-pyrrol-3-yl) ethane **8d***

A solution of nitro derivative **6c,f,i**, **7c** or **8c** (3 mmol) in ethanol 95° (8 mL) was added onto a well-stirred solution of $SnCl_2 \cdot 2H_2O$ (2.48 g, 11 mmol) in concentrated hydrochloric acid (3 mL). The mixture was stirred at room temperature (see table I), treated with water (10 mL) and with 6 N sodium hydroxide until pH 12, then extracted with ethyl acetate (3 x 15 mL). The organic extracts were collected, washed with brine (3 x 30 mL) and dried. Evaporation of solvent gave crude products which were purified on alumina column (ethyl acetate as eluent) to give pure **6j,k,l**, **7d** or **8d**.

*Nitrate salts of **6a–e,g–l**, **7d** and **8d***

Nitric acid (90%; 0.14 mL, 210 mg, 3 mmol) was added dropwise to an ice-cooled solution of imidazole derivative (**6a–e**, **6g–l**, **7d**, **8d**) (3 mmol) in isopropyl alcohol (1 mL). After stirring at room temperature for 1 h, isopropyl ether was added and the suspension was stirred at room temperature for 15 h. The precipitate was filtered and recrystallized from suitable solvent (see table I).

Antimycotic assays

Test compounds were dissolved in DMSO at an initial concentration of 100 mg/mL and then serially diluted in culture medium. Cell lines were from American Type Culture Collection (ATCC); fungal strains were obtained either from ATCC or were clinical isolates from Clinica Dermosifilopatica, University of Cagliari. Yeast blastopores were obtained from a 30-h-old shaken culture incubated at 30 °C in Sabouraud dextrose broth, whereas the dermatophyte inoculum was scraped aseptically with a spatula from a 7-day-old agar culture. The macerate was then finely suspended in Sabouraud dextrose broth using a glass homogenizer. Glycerol, final concentration 10%, was added as cryoprotective agent to both the yeast and the dermatophyte suspensions, aliquots of which were then stored in liquid nitrogen. Test tubes were inoculated with 10^3 blastopores or colony forming units (CFU)/millilitre. The minimal inhibitory concentration (MIC) was determined by serial dilutions using Sabouraud dextrose broth (pH 5.7) and incubating at 37 °C. The growth control for yeasts was read after 1 day and for dermatophytes after 2 days. The MIC was defined as the compound concentration at which no macroscopic signs of fungal growth were detectable.

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