

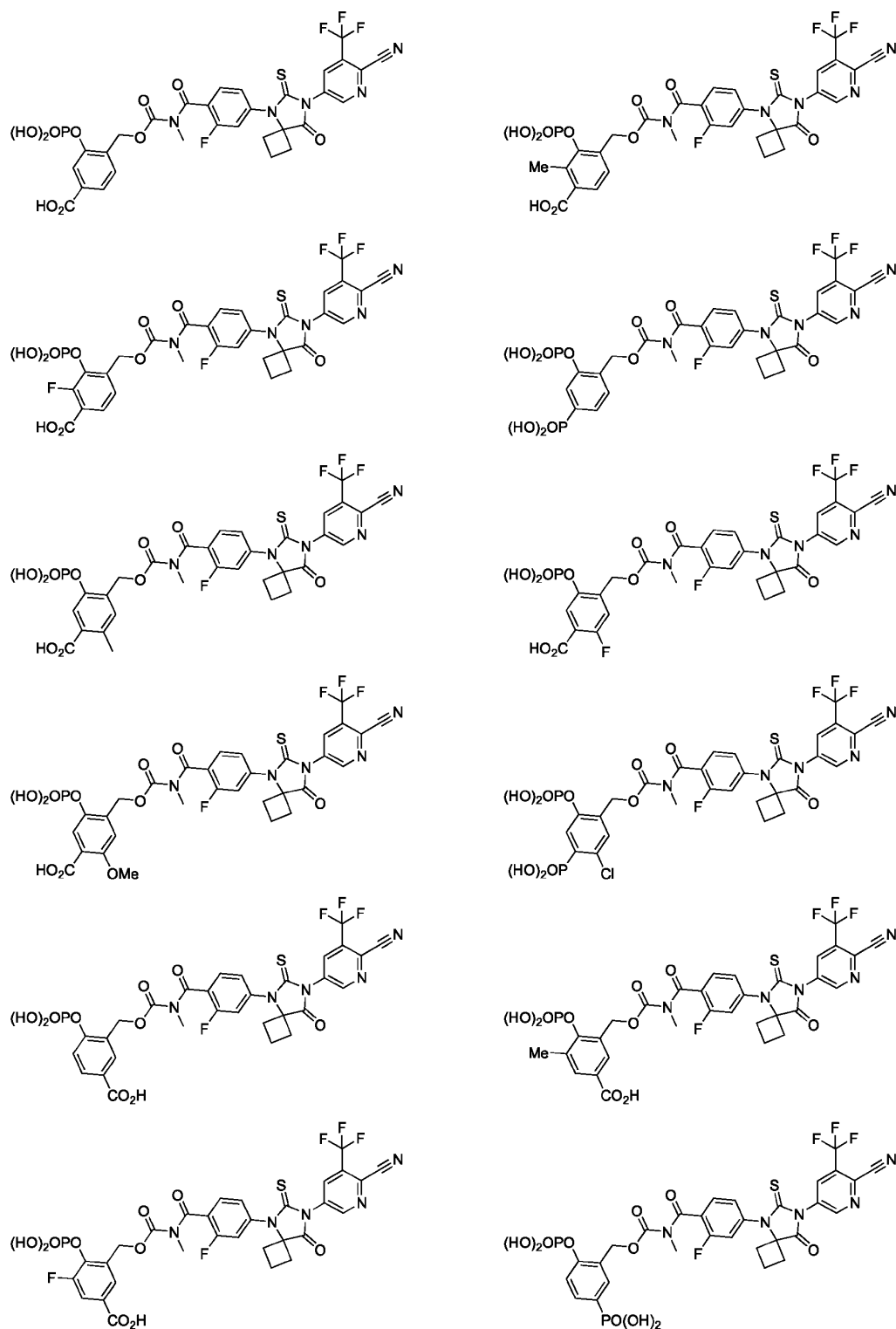


FIG. 1
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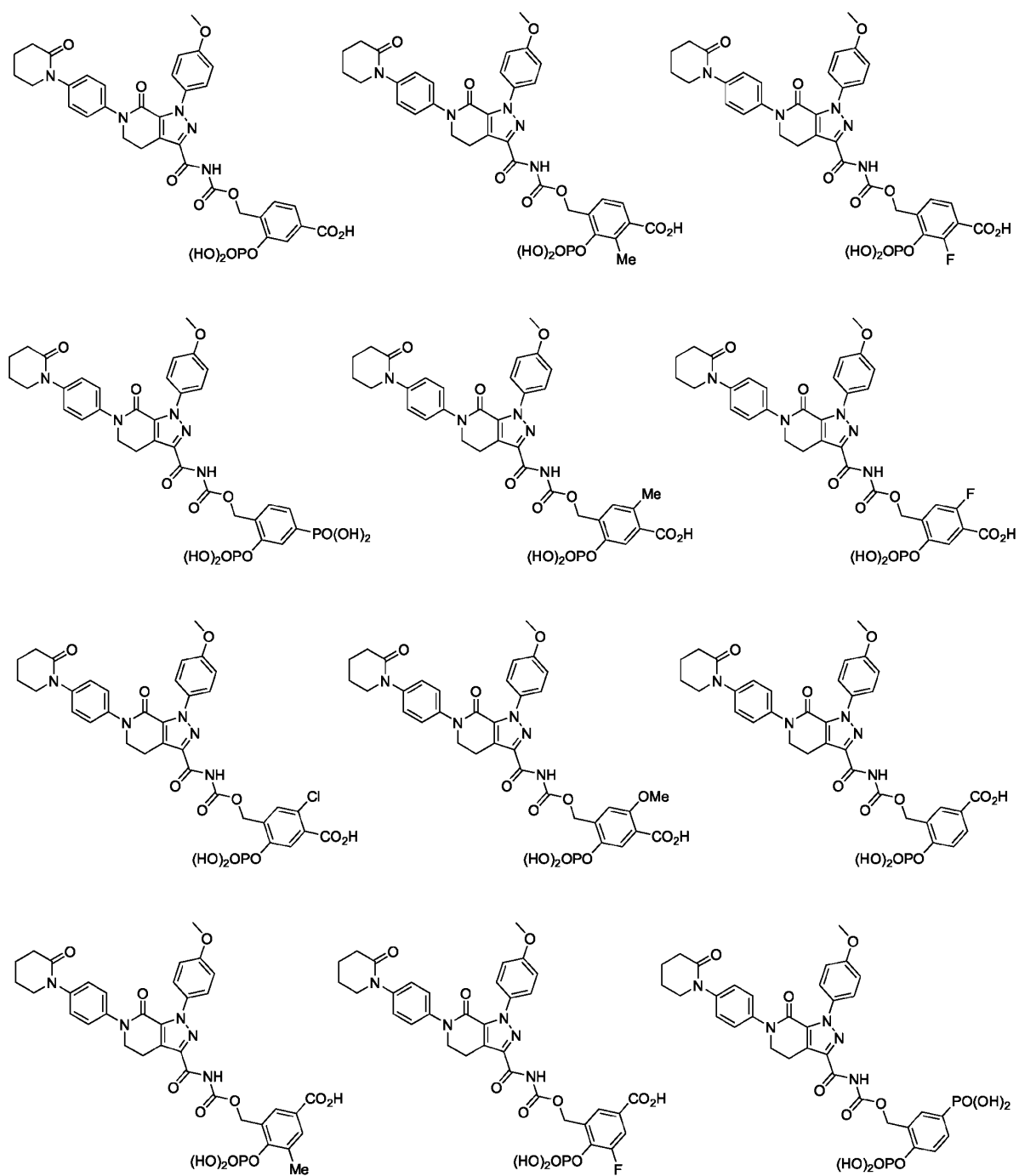


FIG. 2

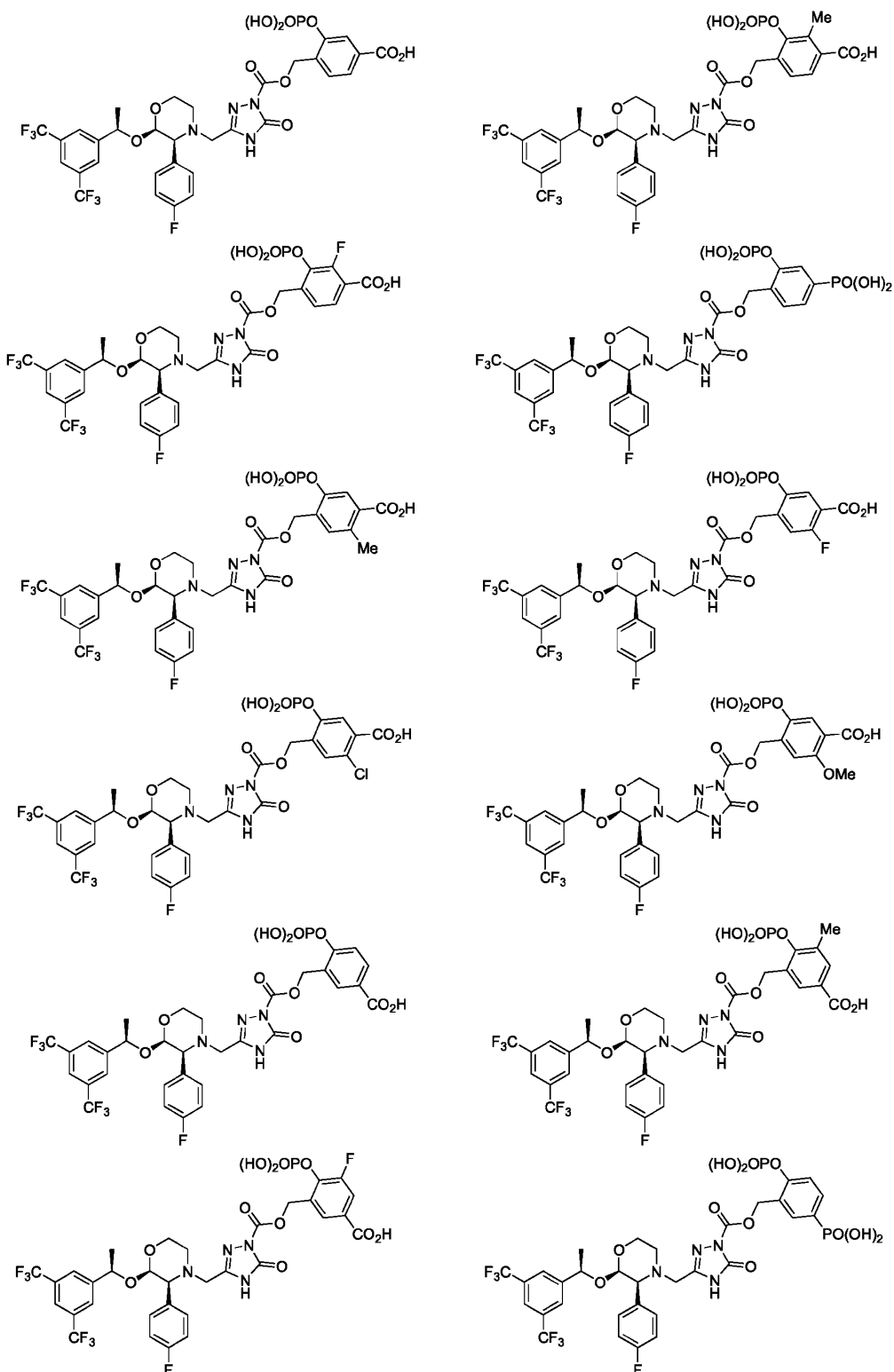


FIG. 3
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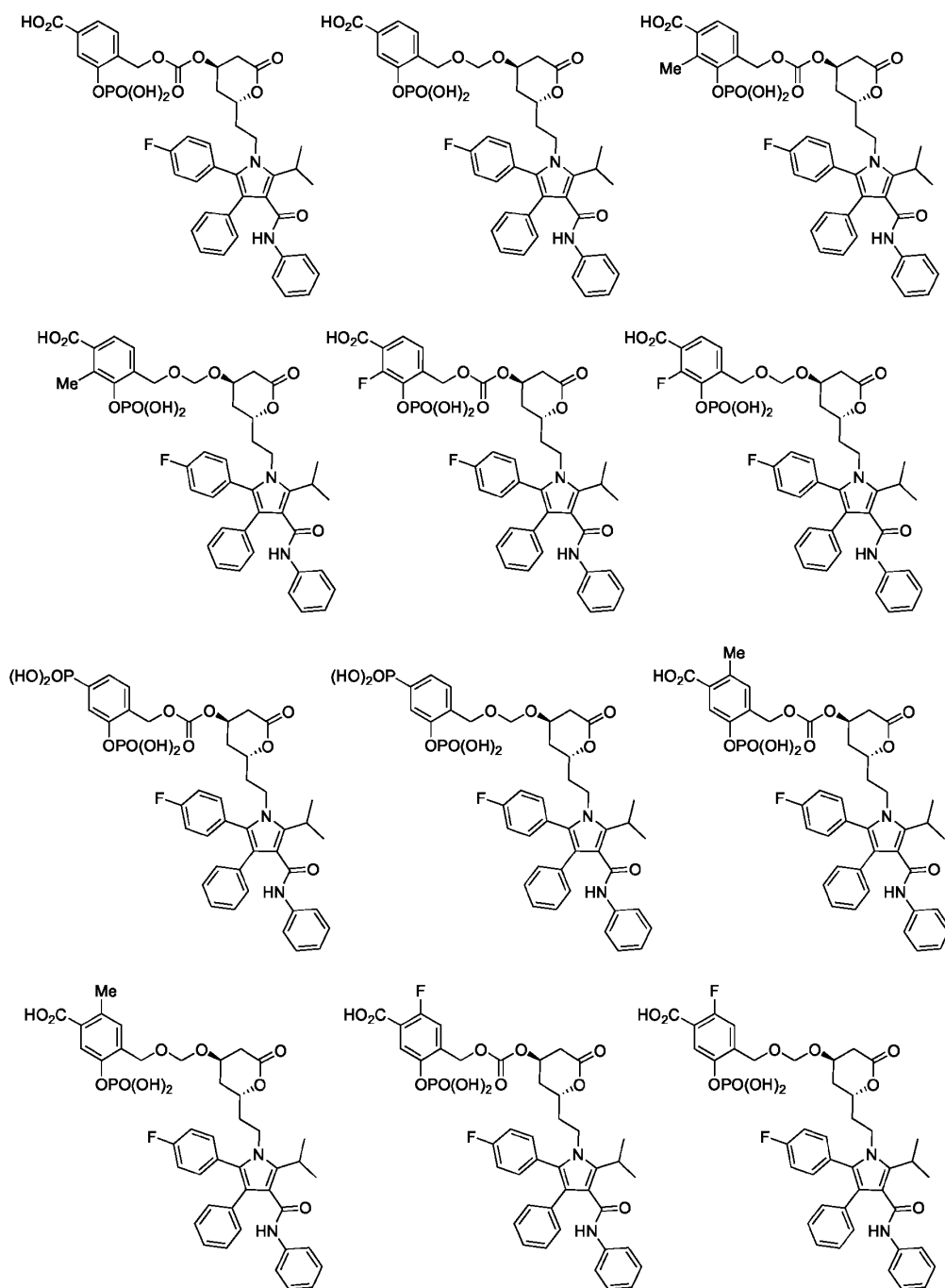


FIG. 4A

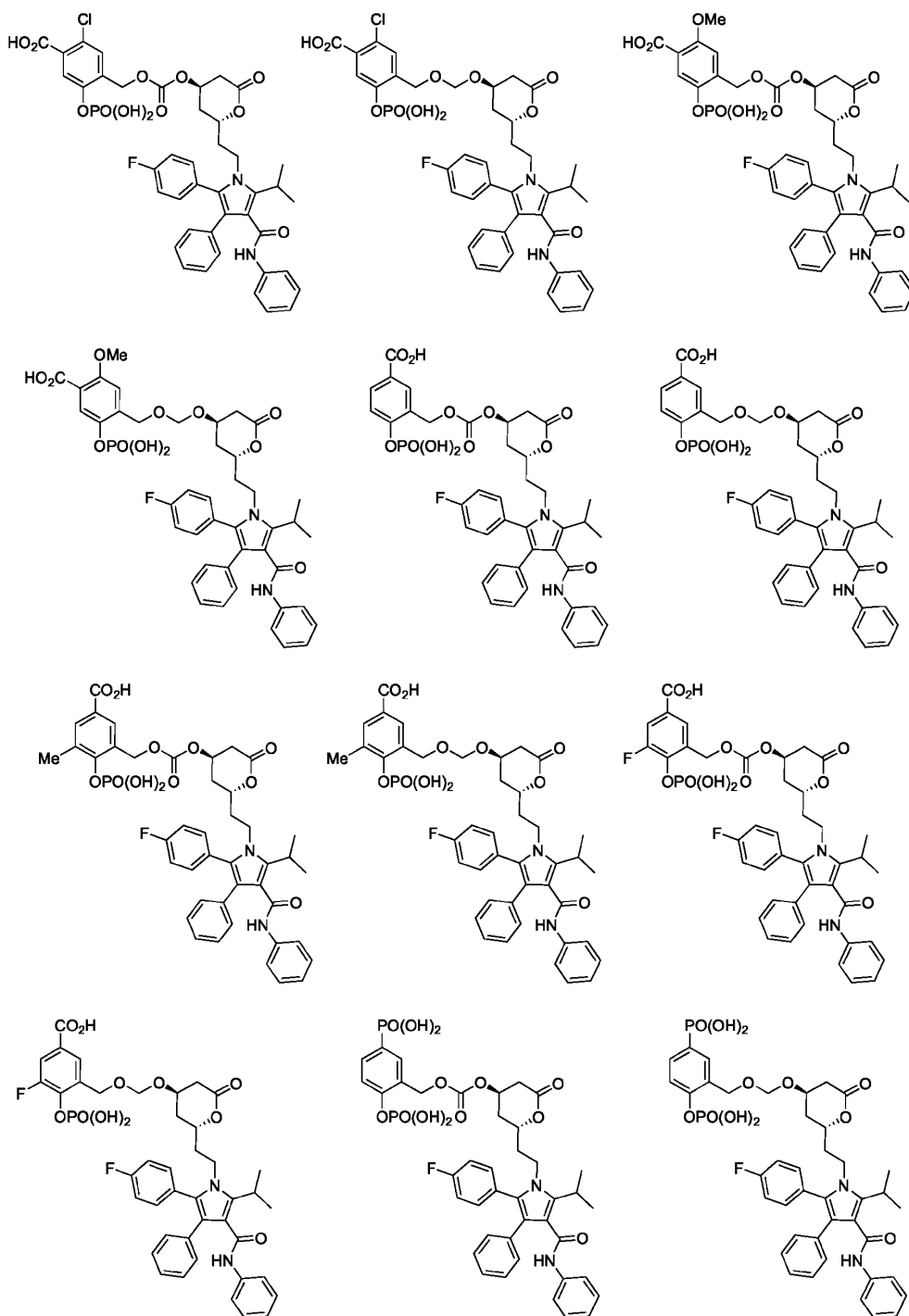


FIG. 4B

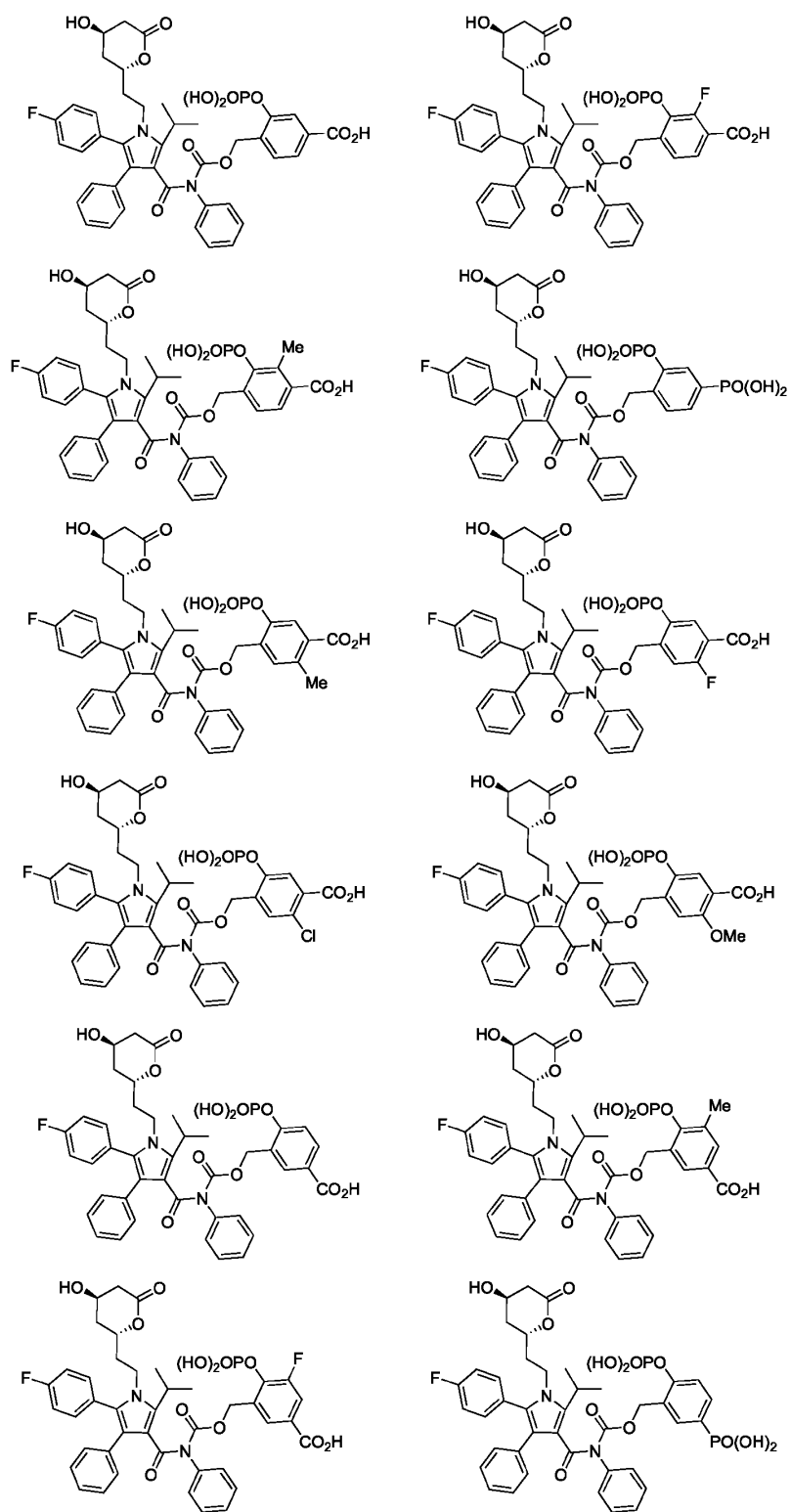


FIG. 4C
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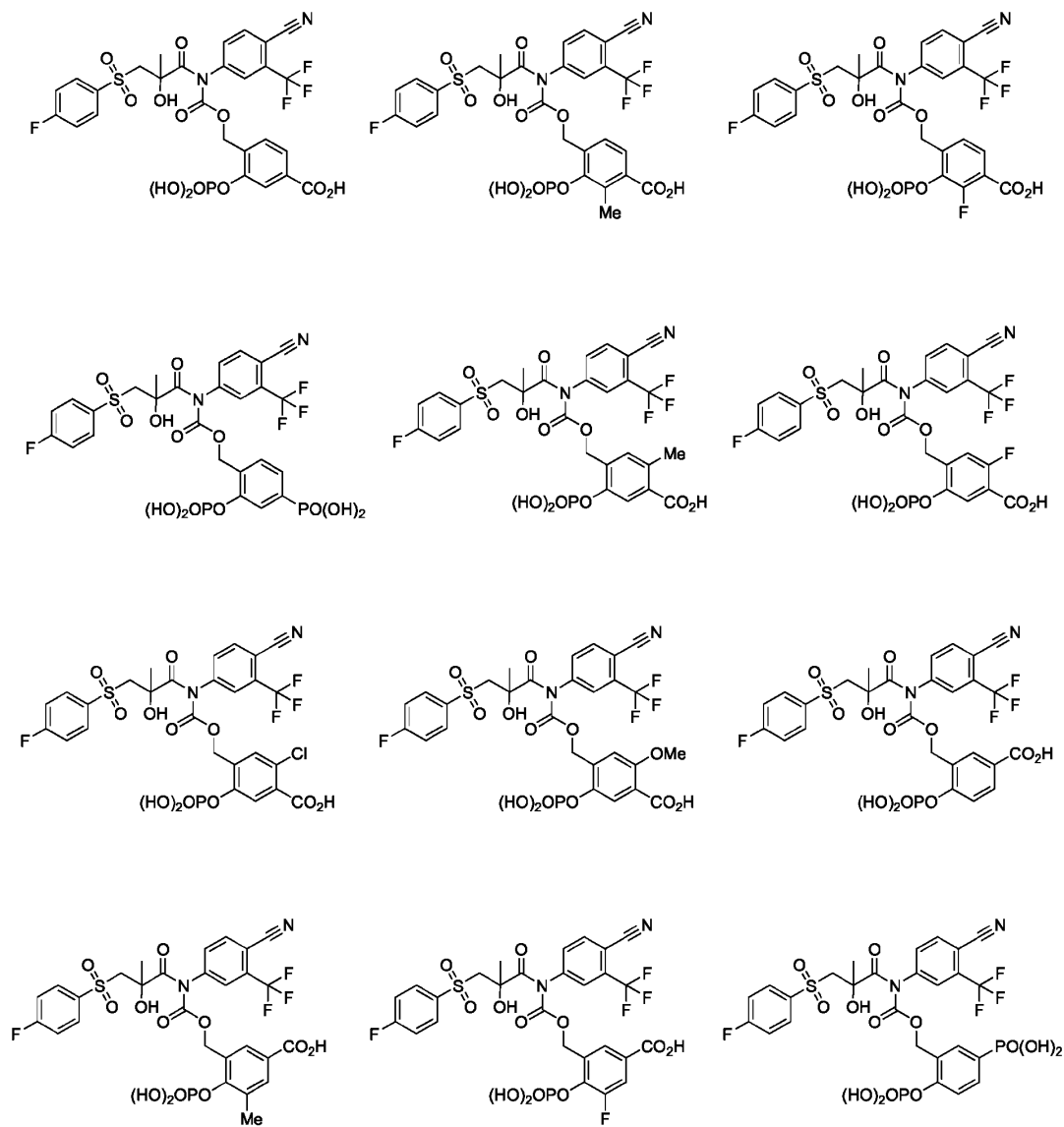


FIG. 5



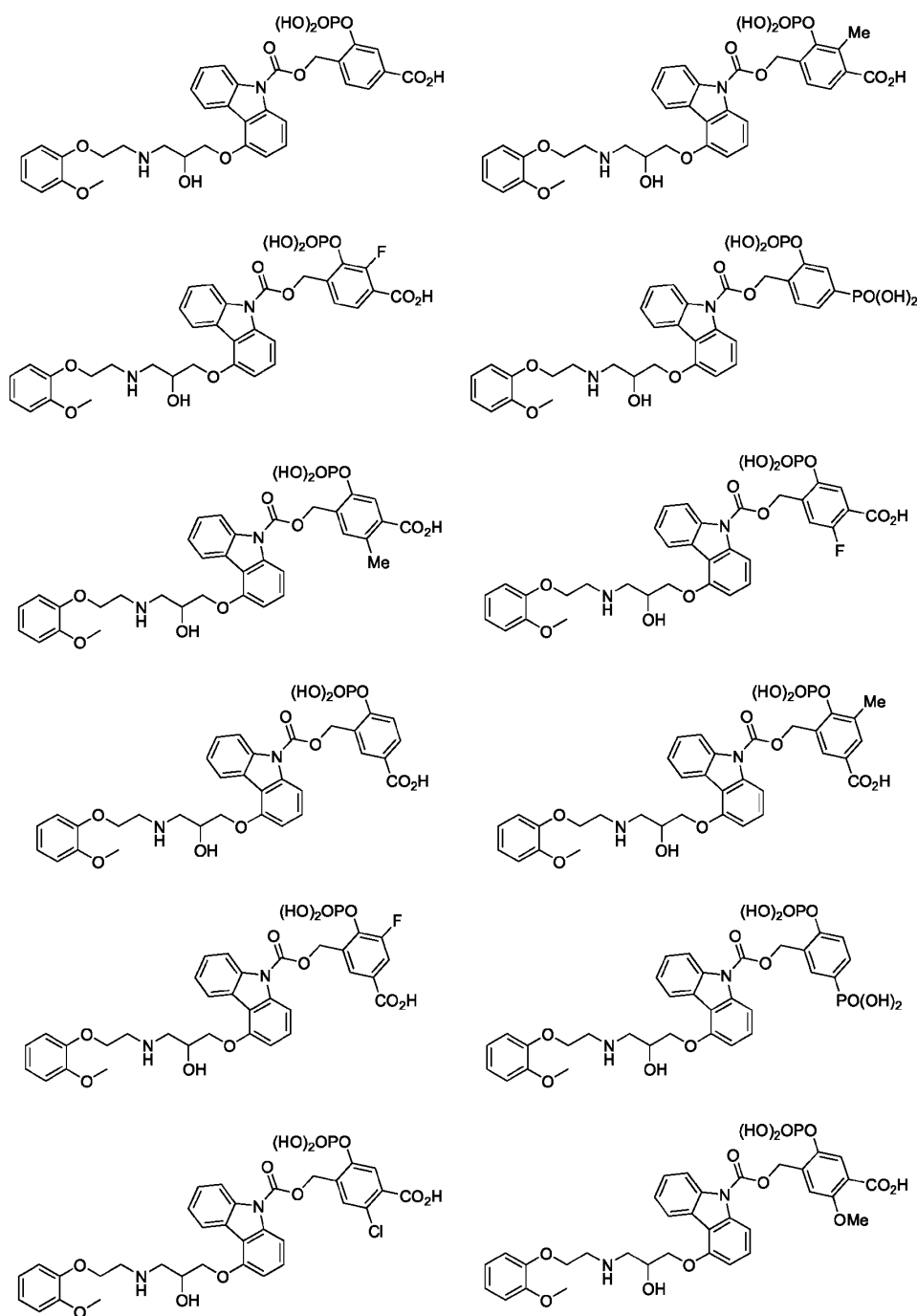


FIG. 6B

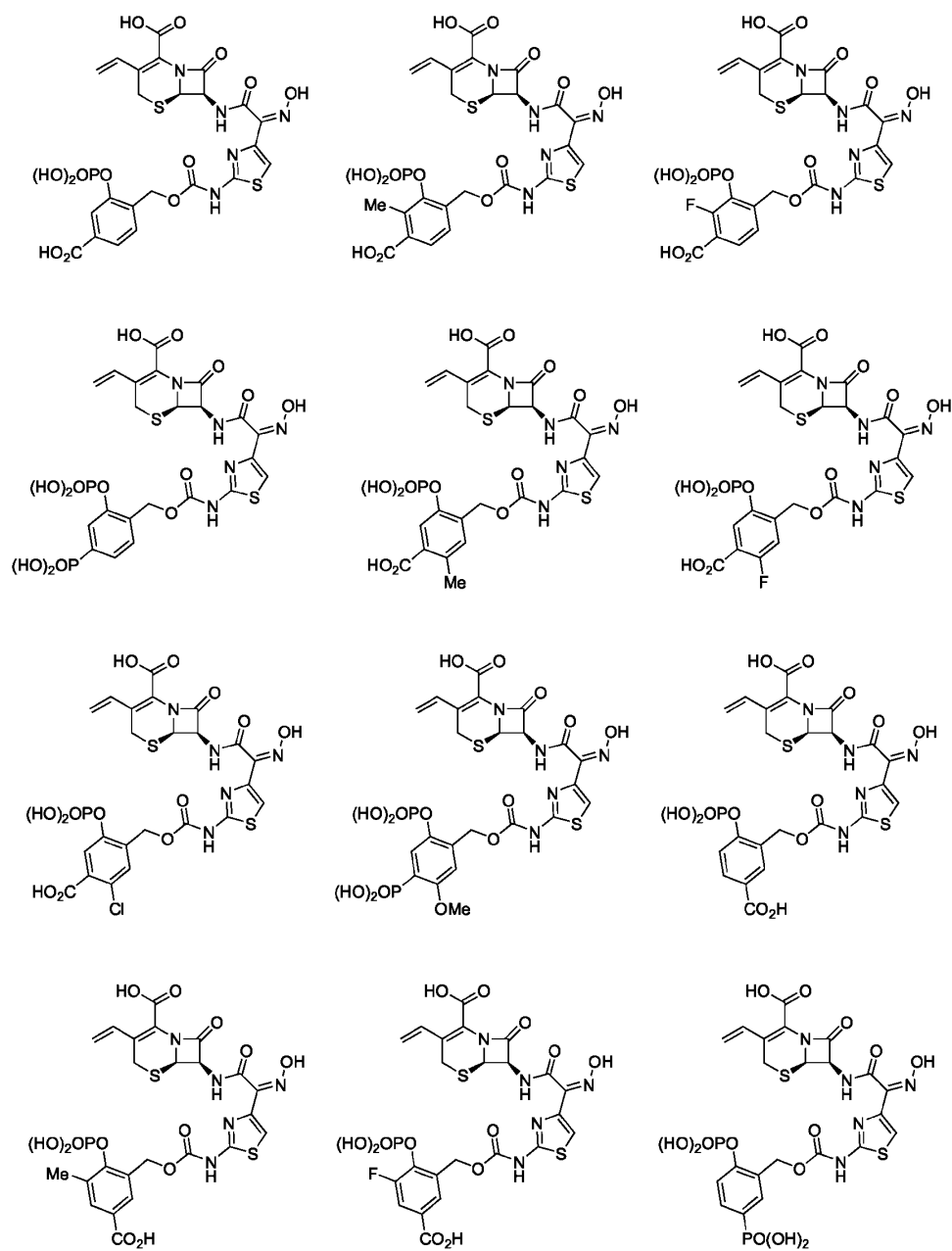


FIG. 7

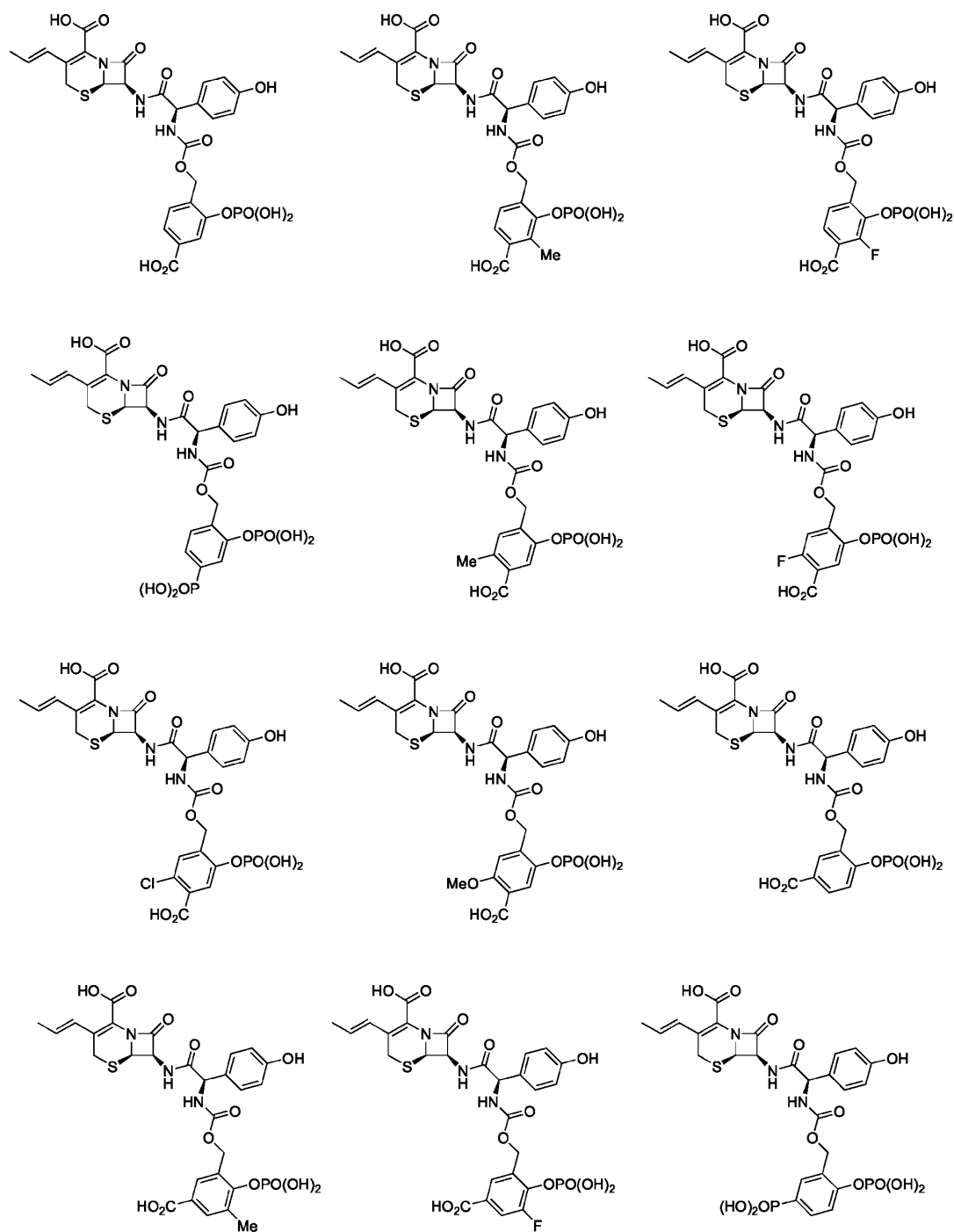


FIG. 8

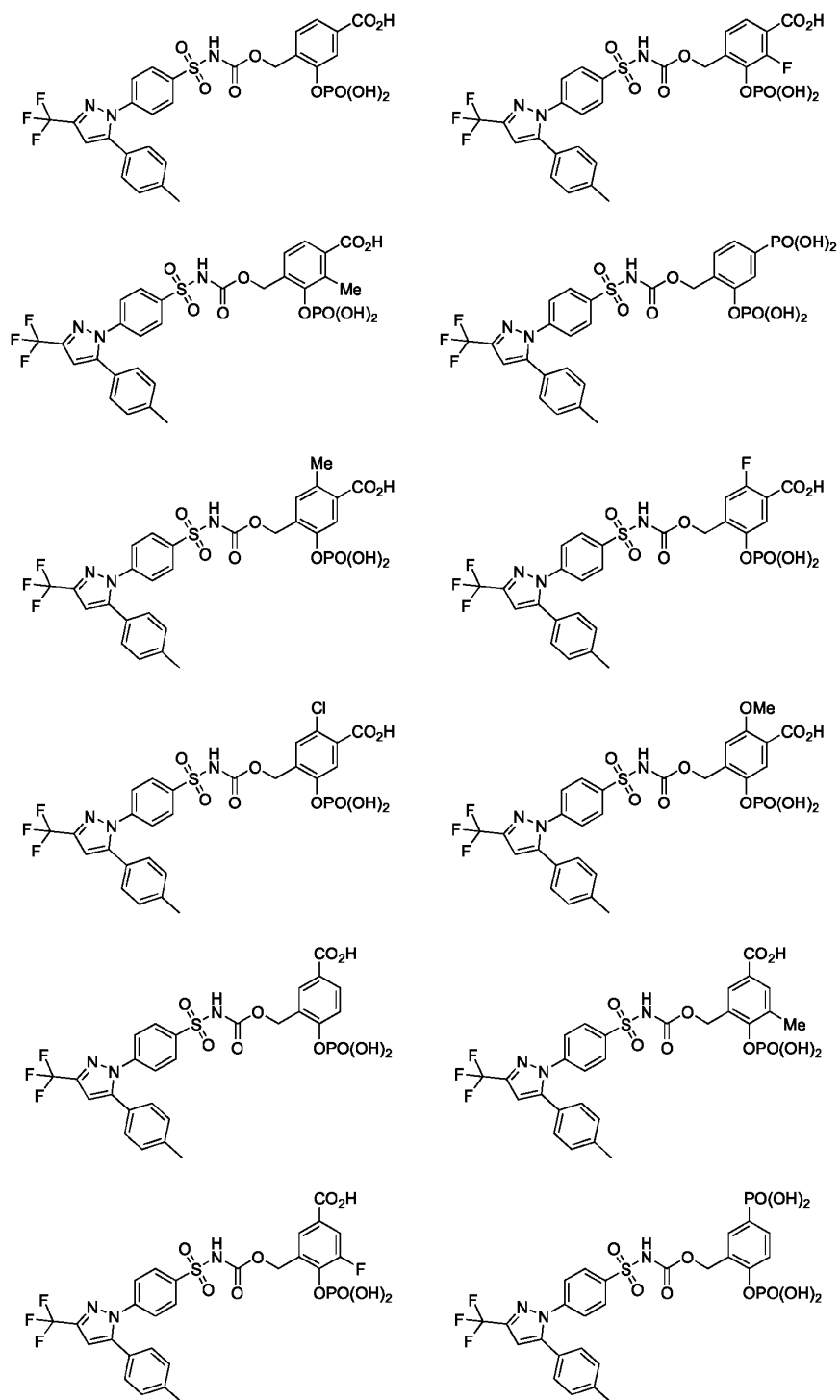


FIG. 9

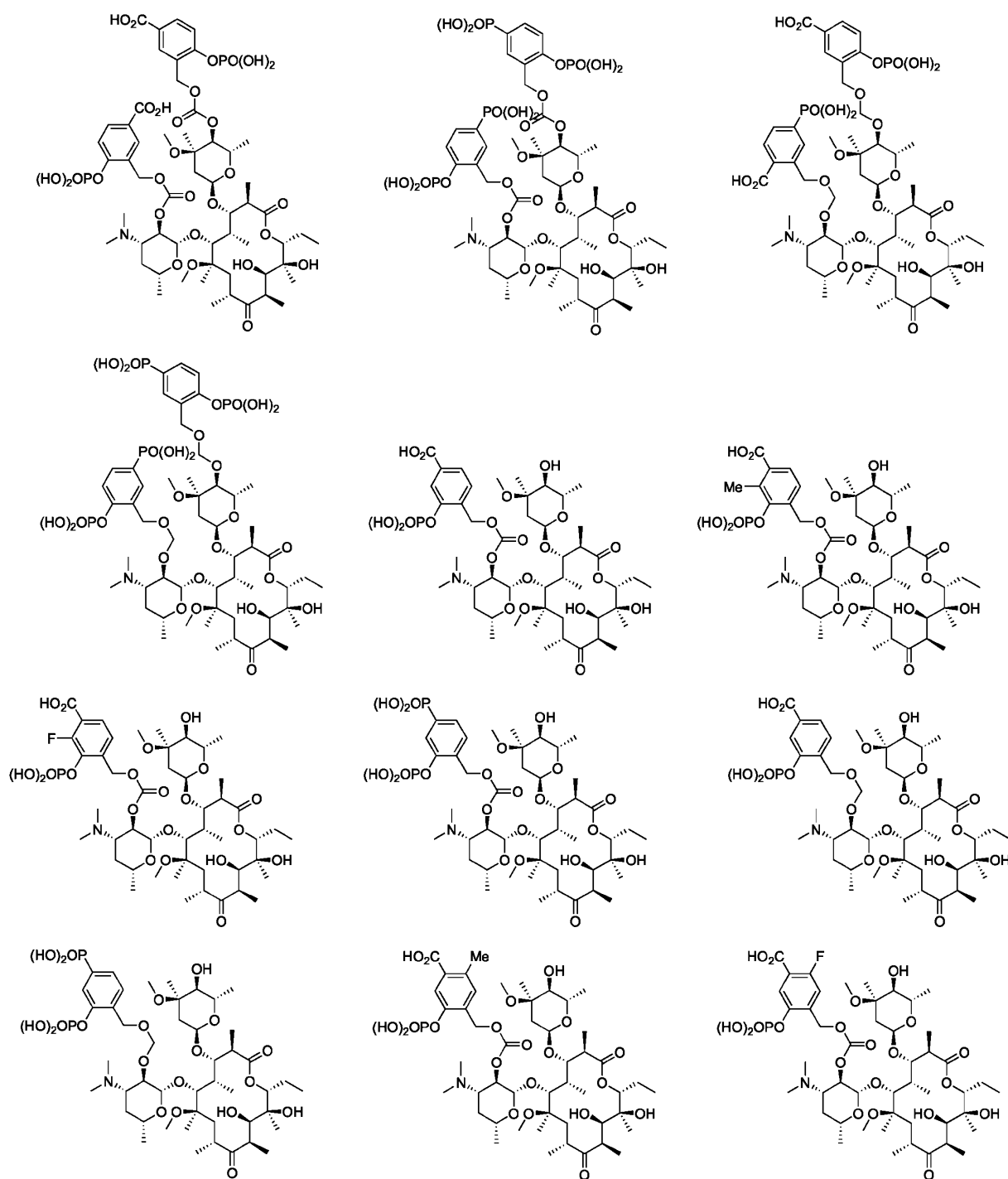


FIG. 10A

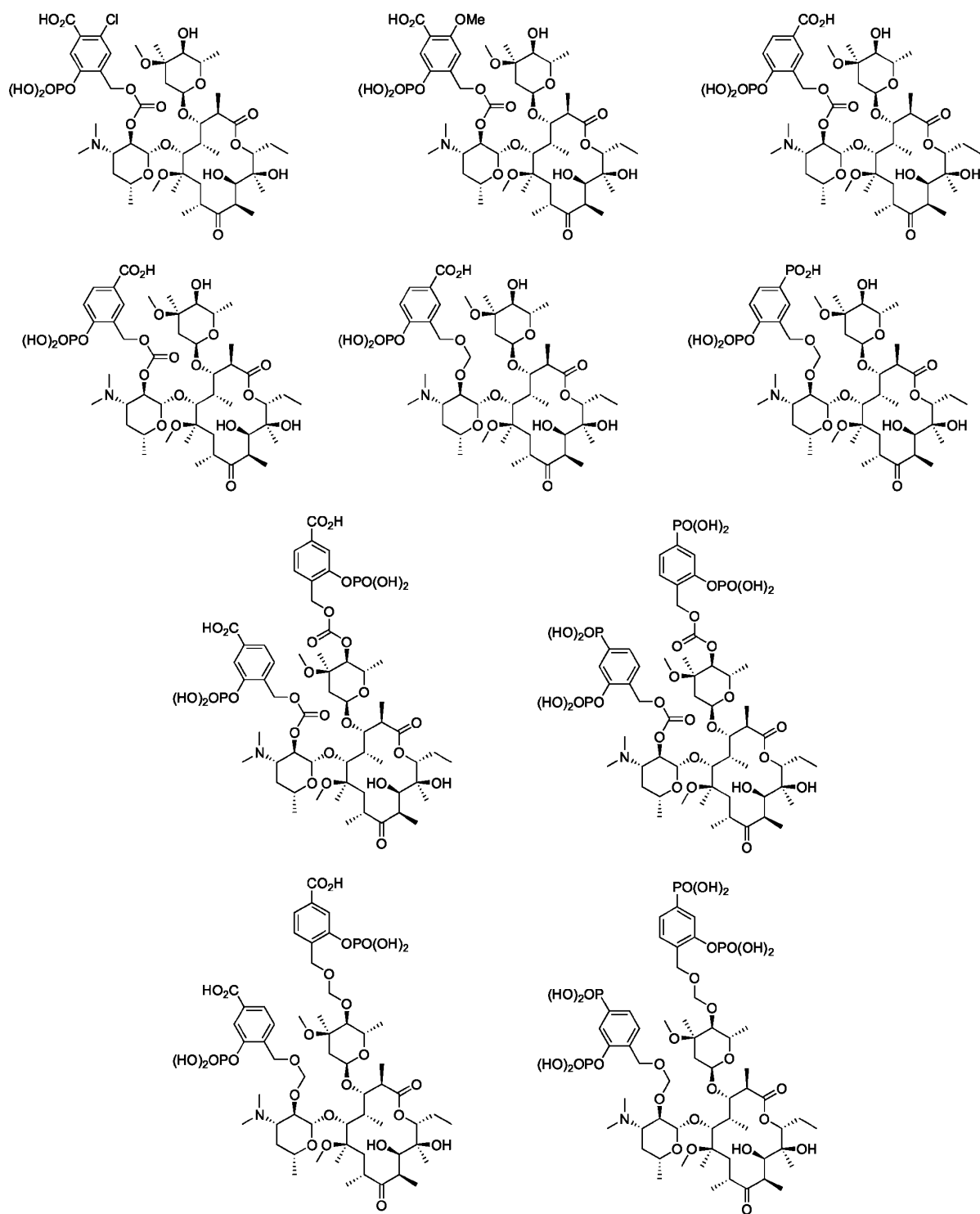


FIG. 10B



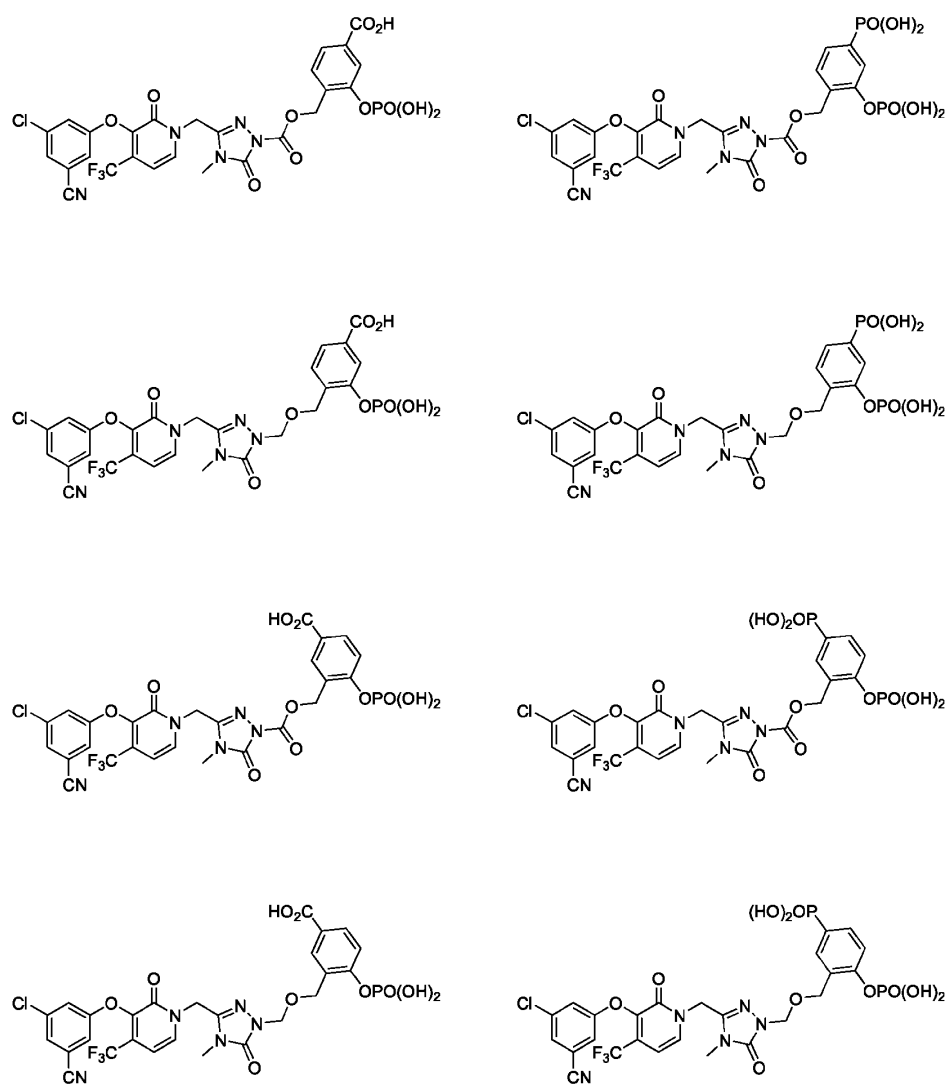


FIG. 12

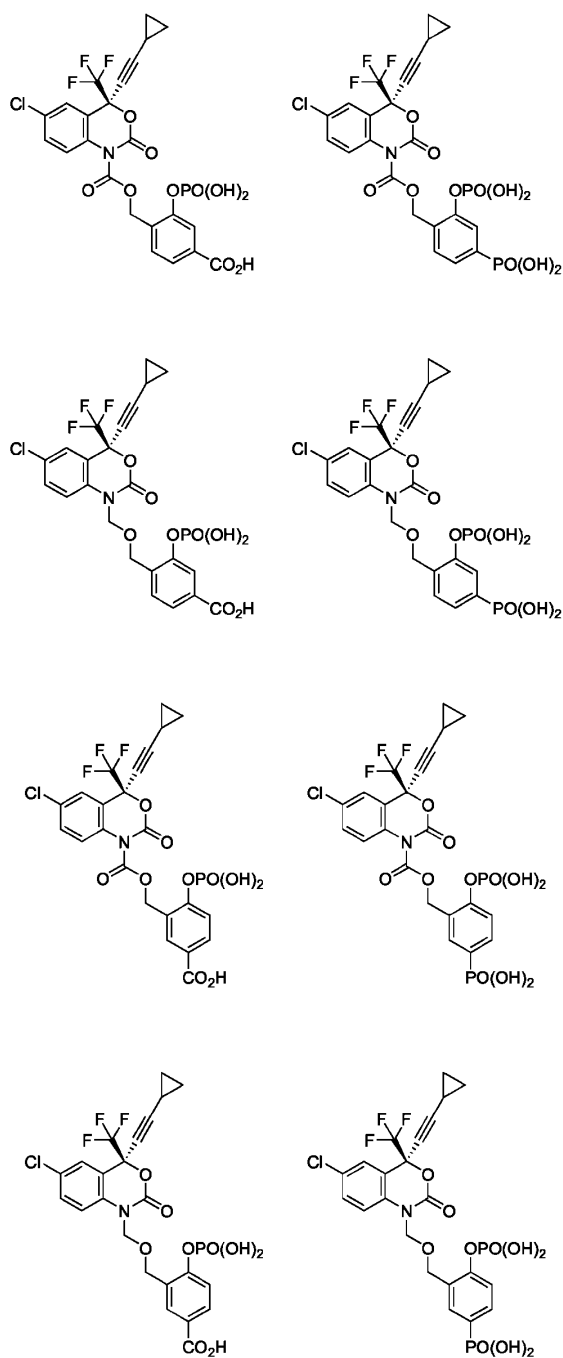


FIG. 13

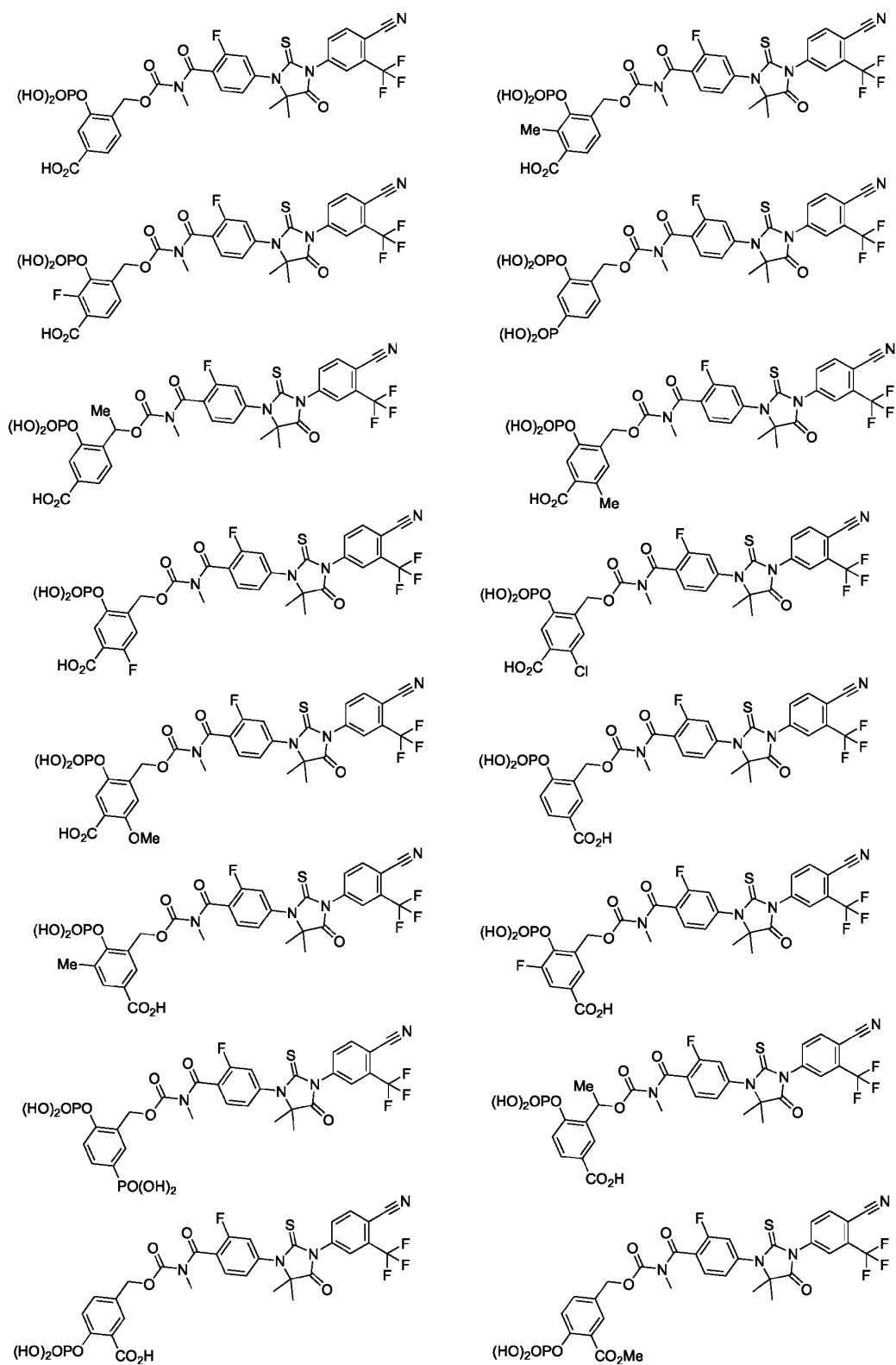


FIG. 14
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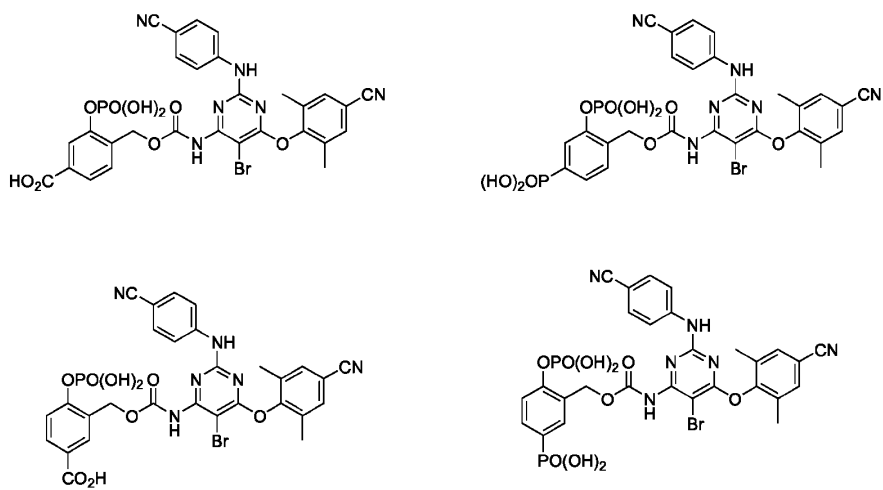


FIG. 15

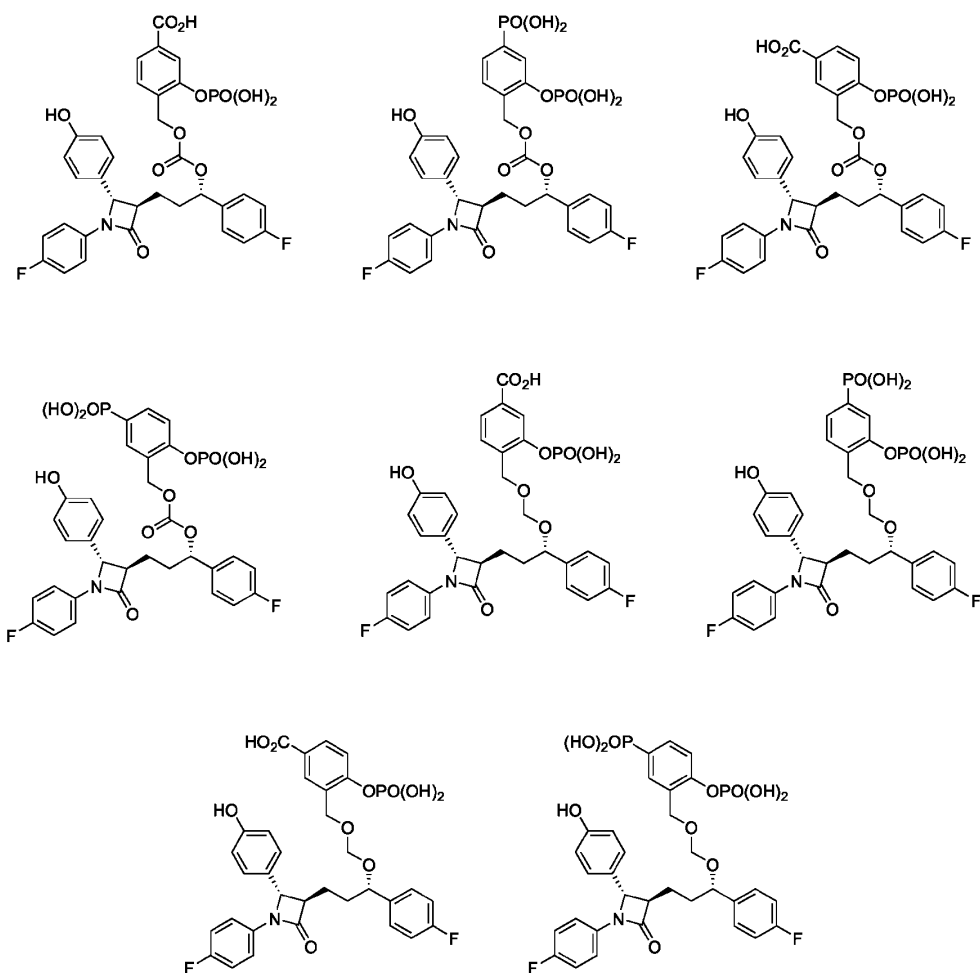


FIG. 16

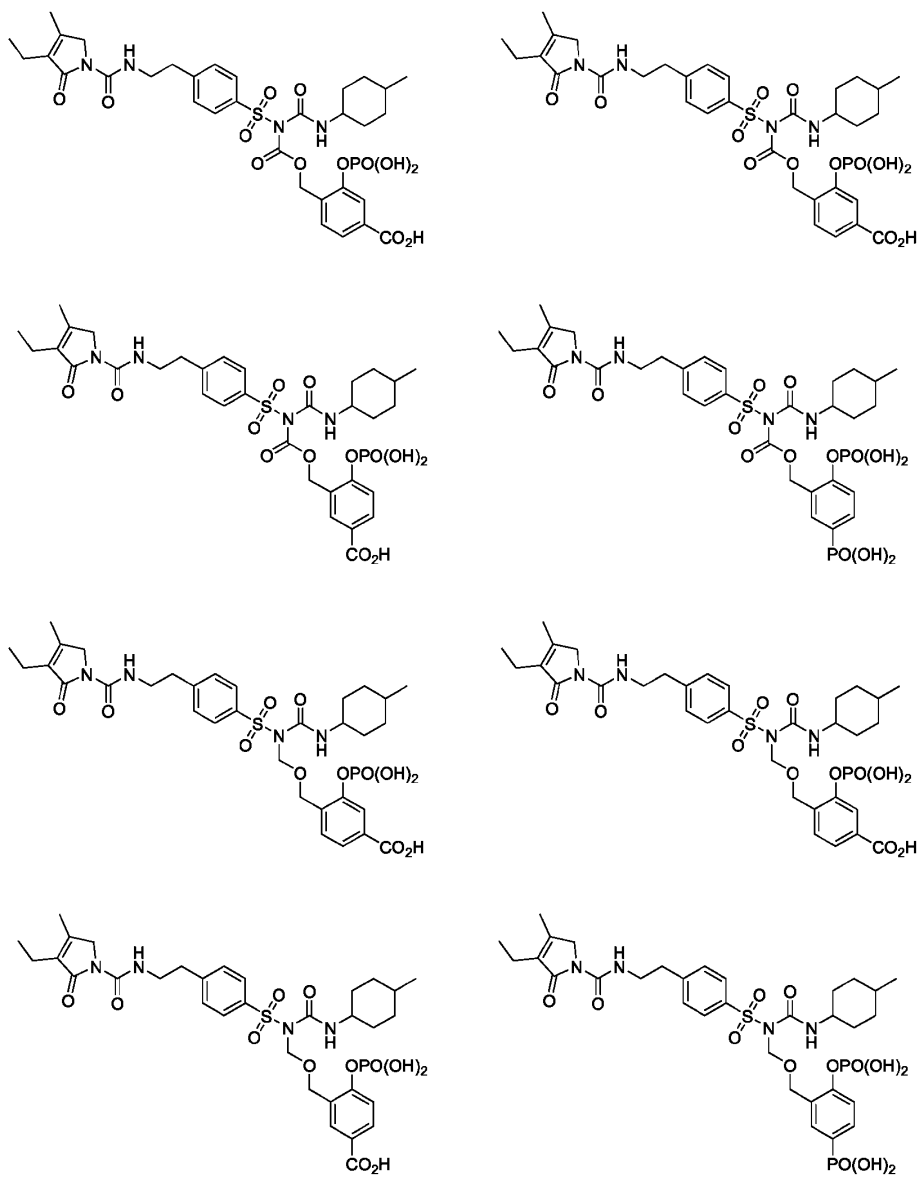


FIG. 17

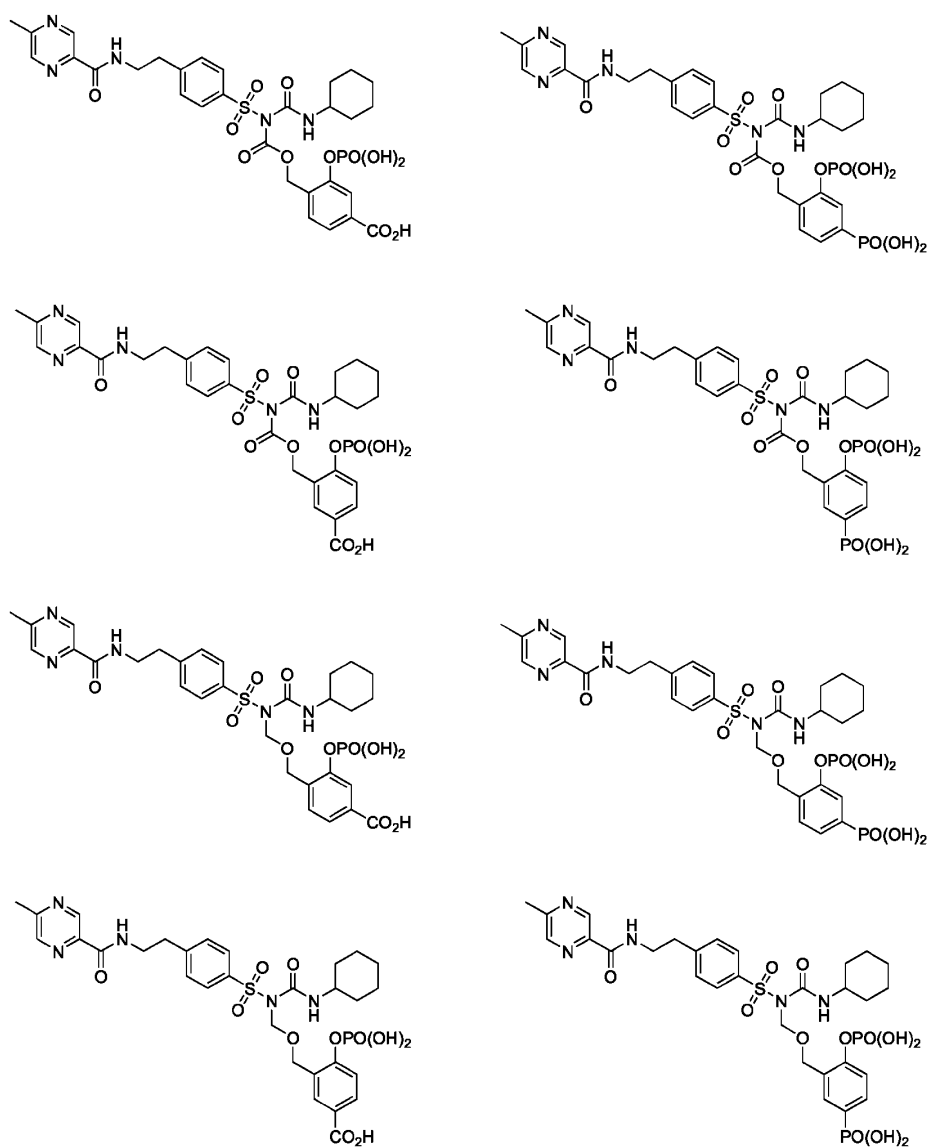


FIG. 18

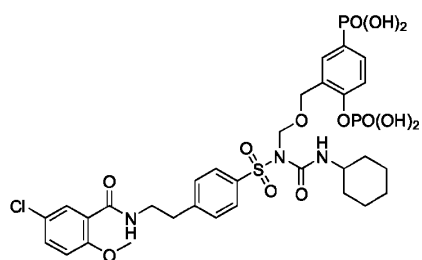
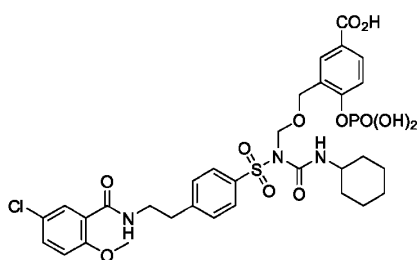
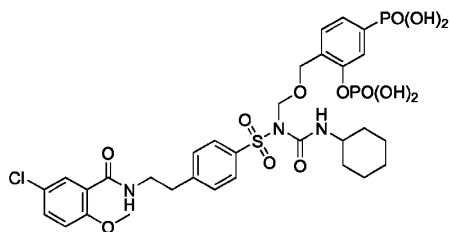
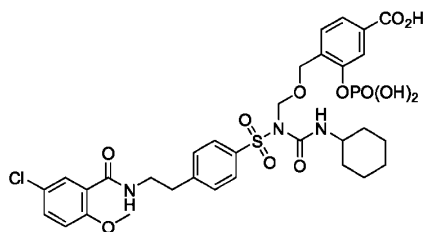
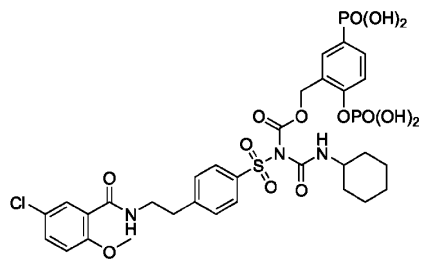
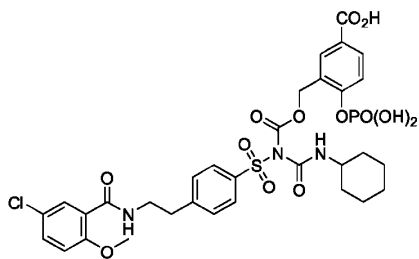
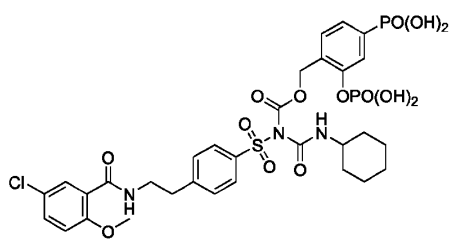
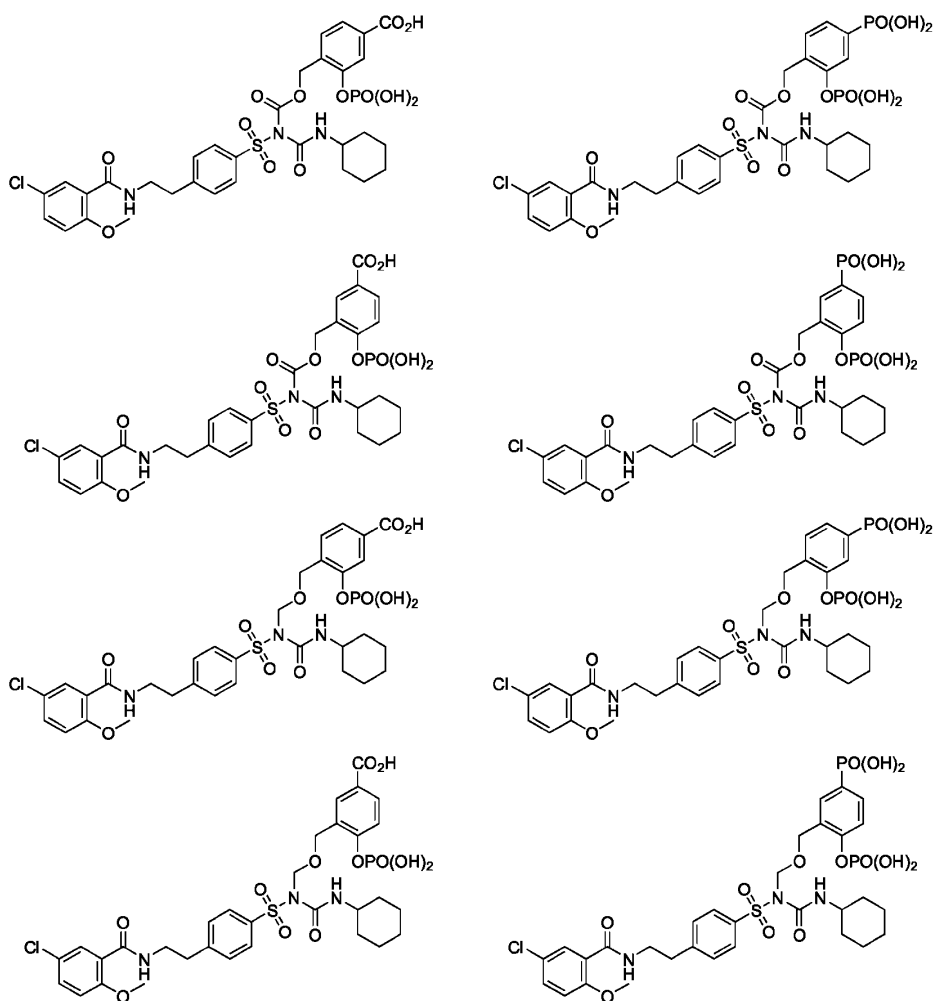


FIG. 19

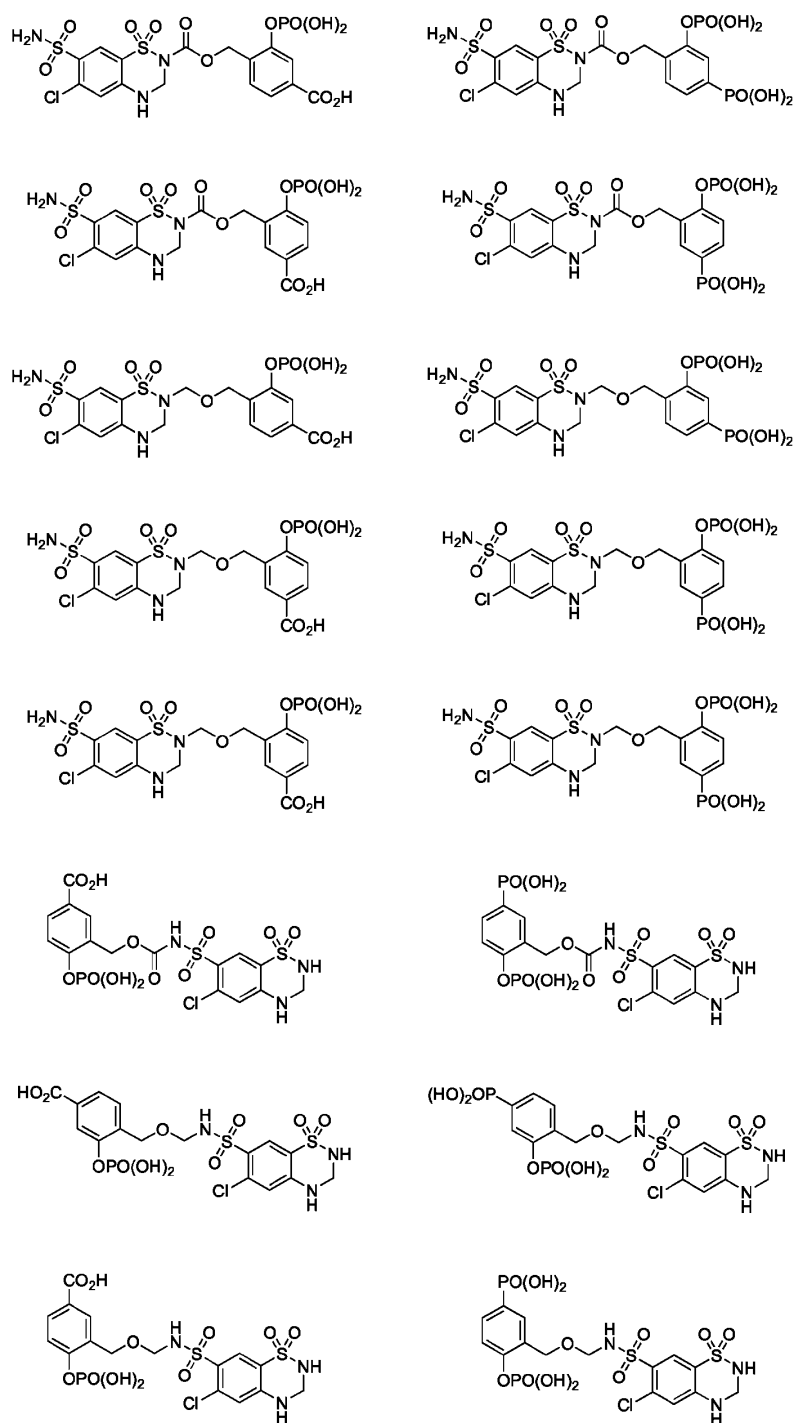


FIG. 20

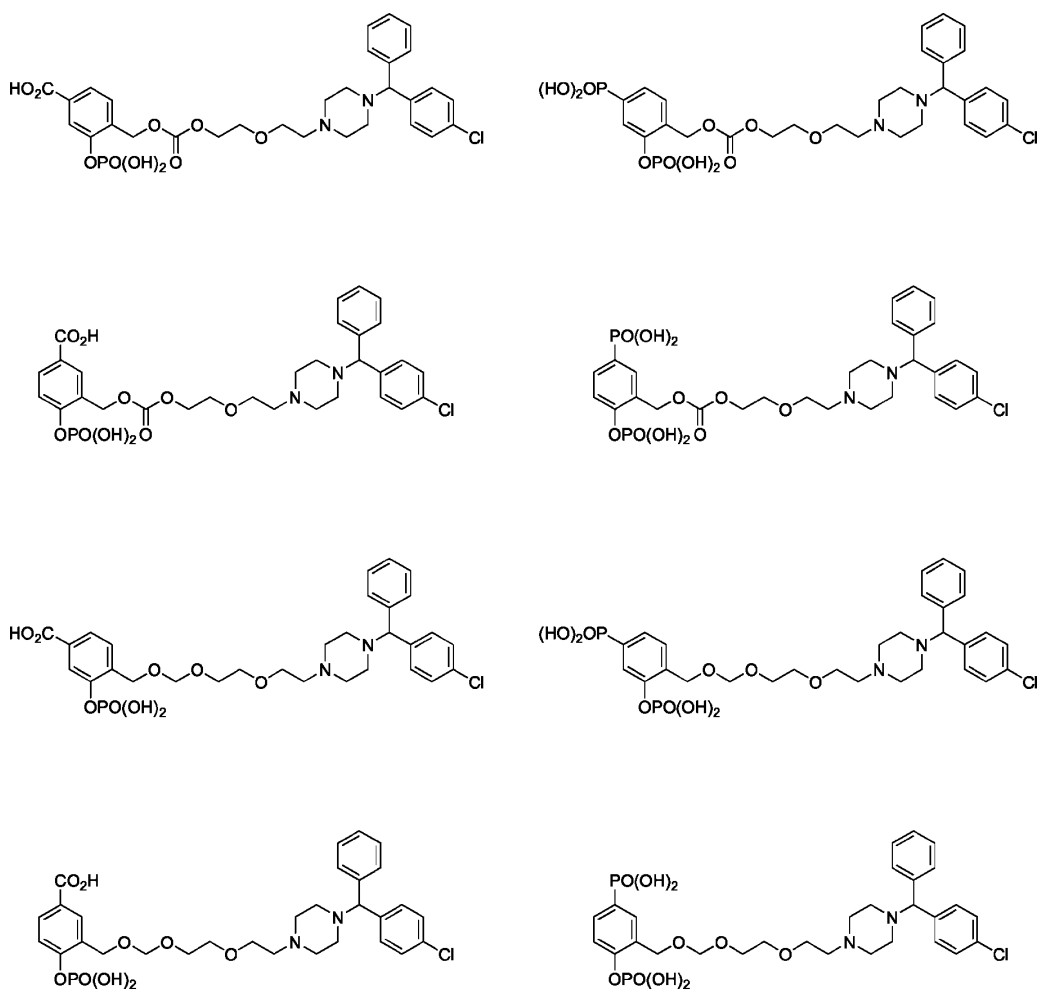


FIG. 21

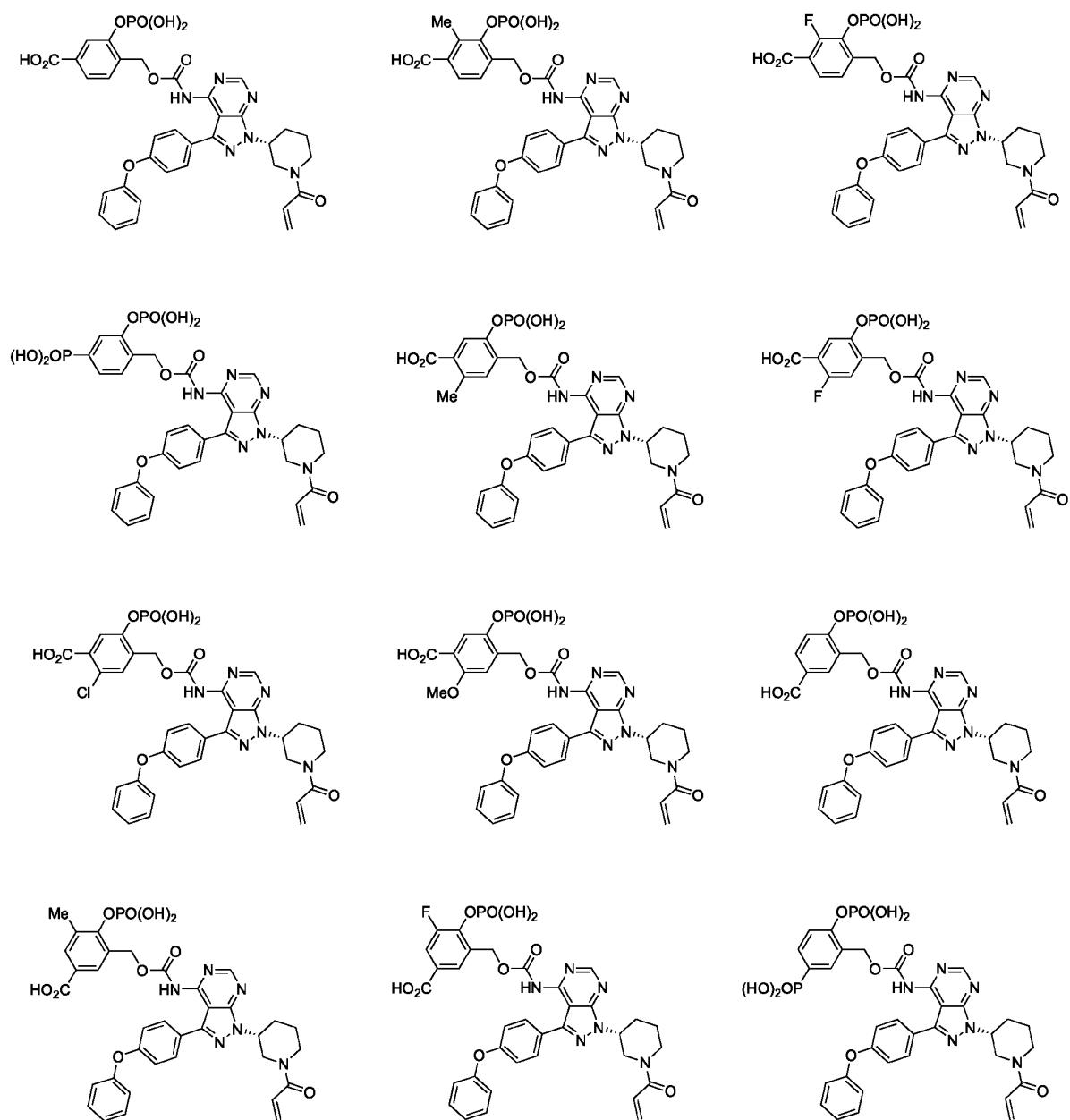


FIG. 22

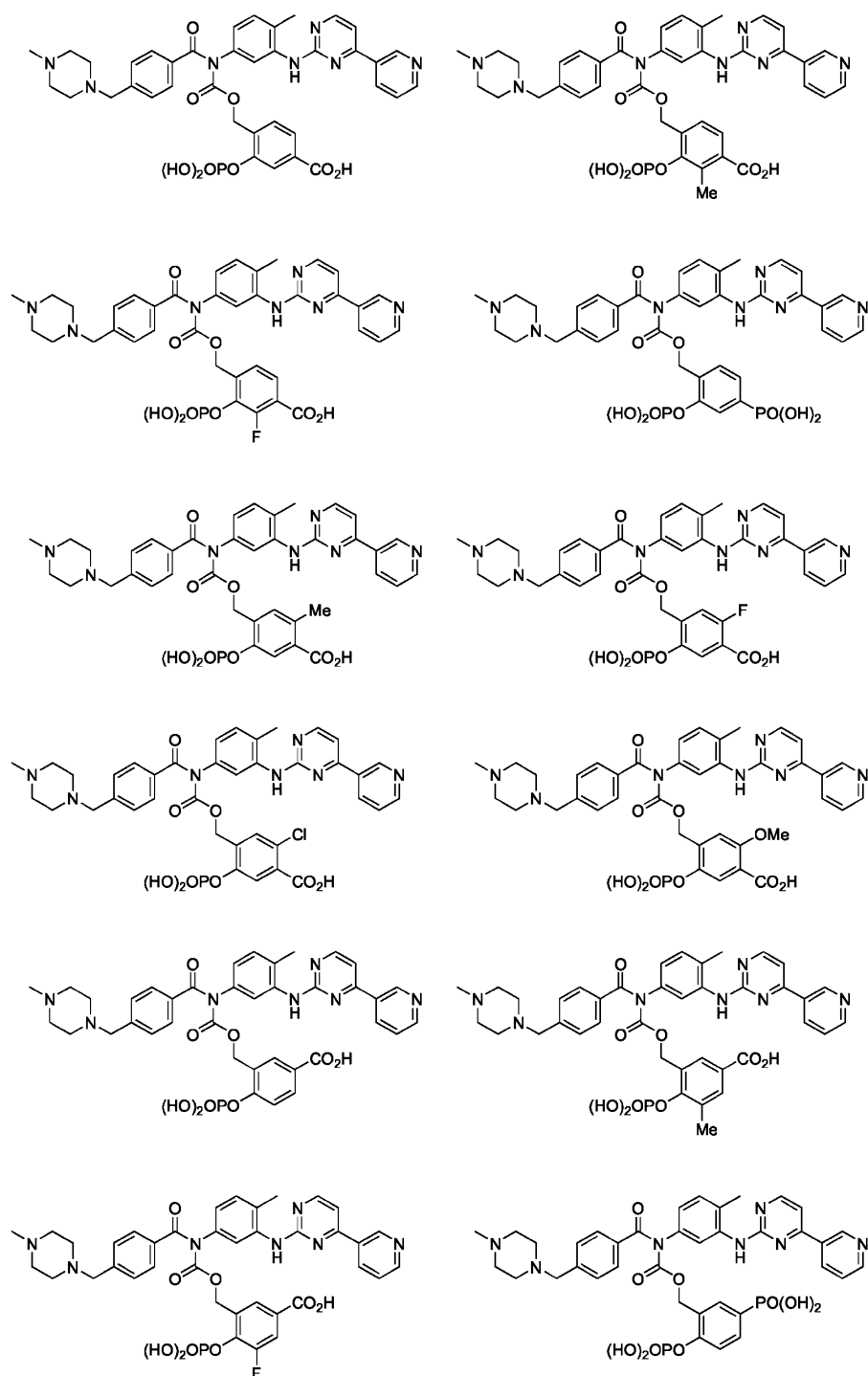


FIG. 23

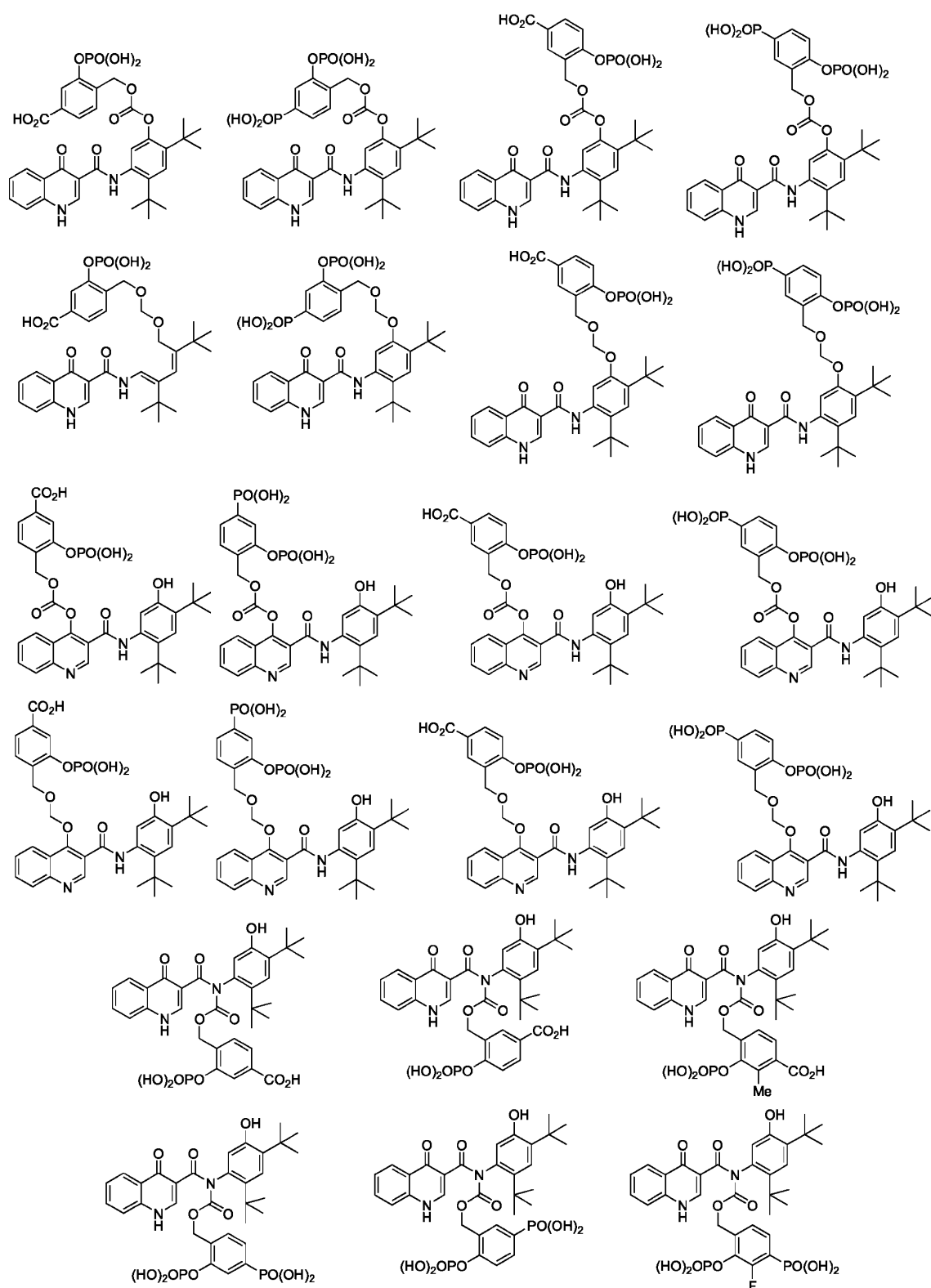


FIG. 24
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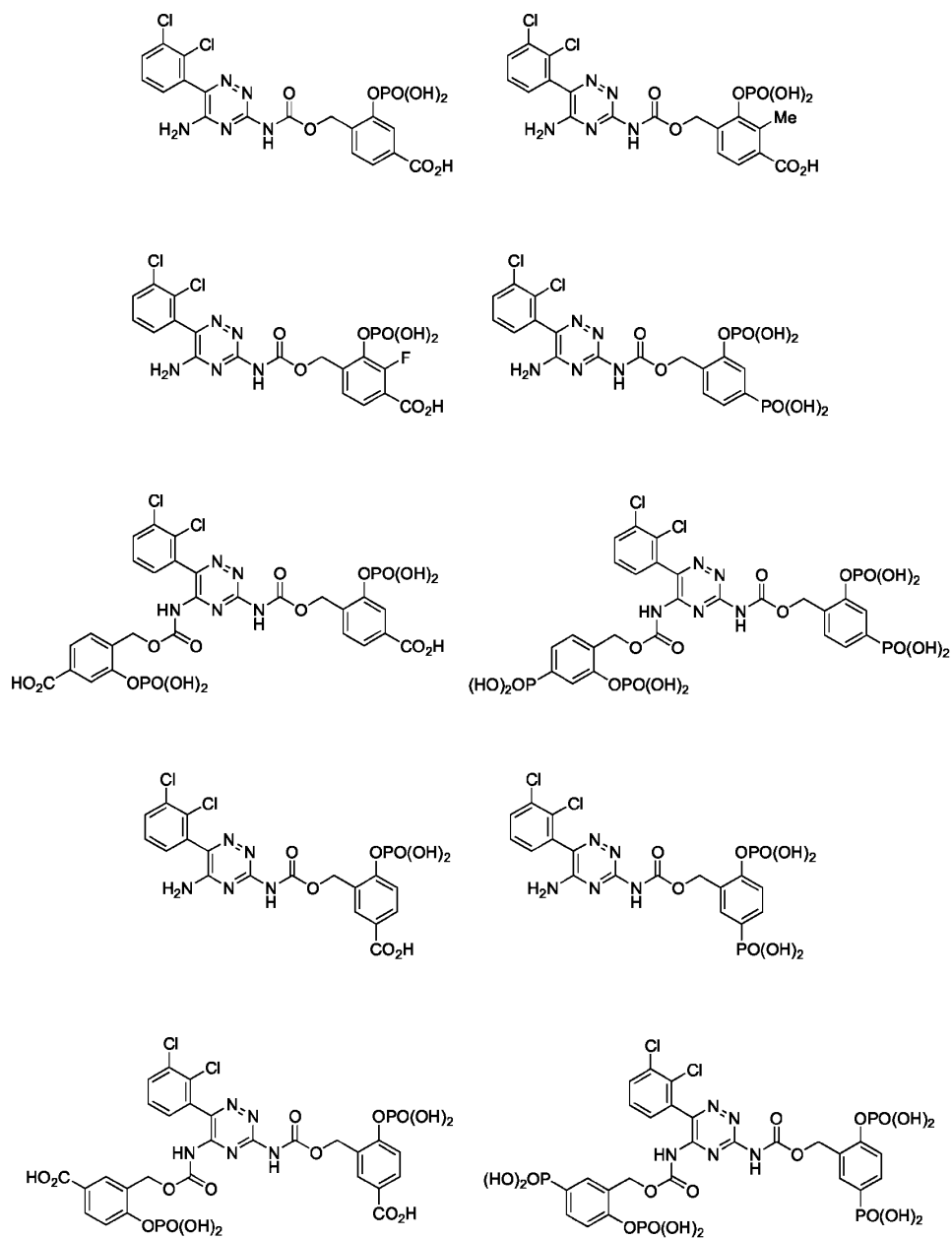


FIG. 25

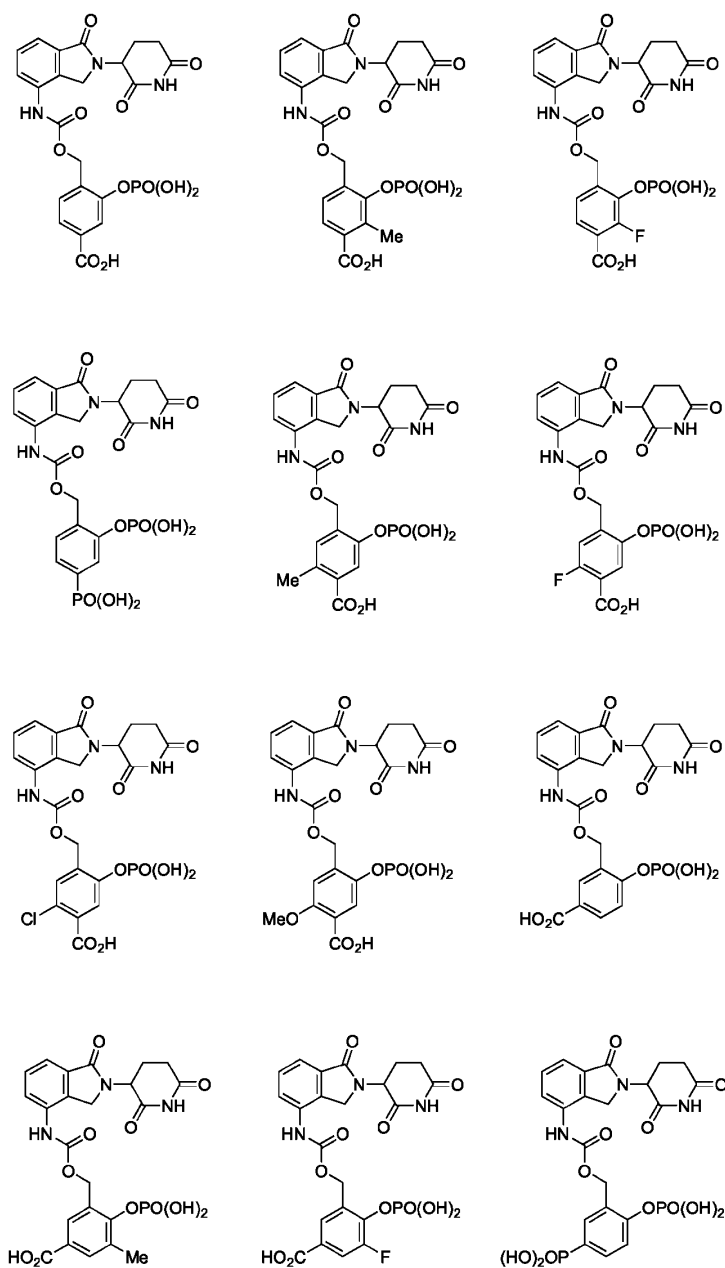
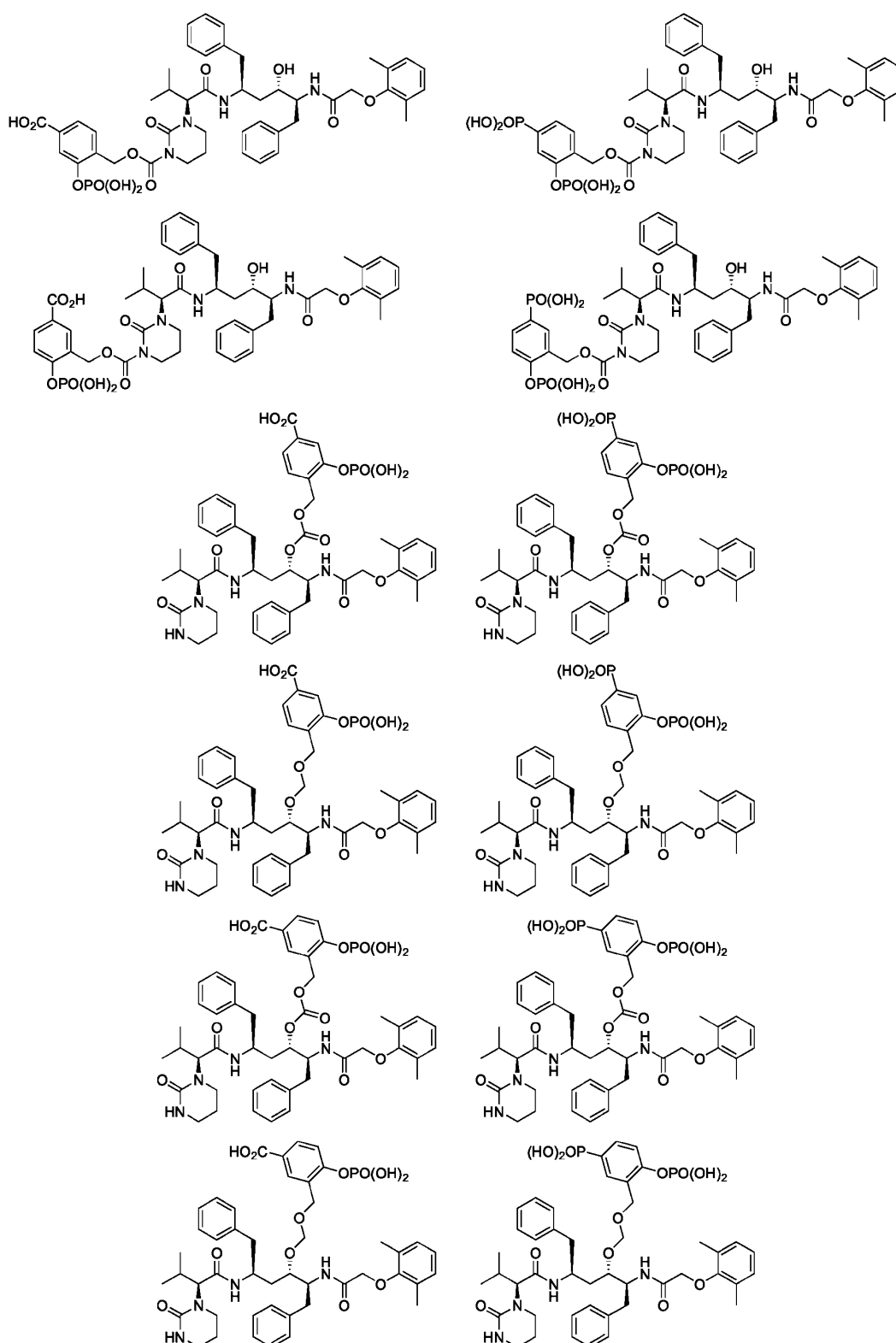


FIG. 26

**FIG. 27**
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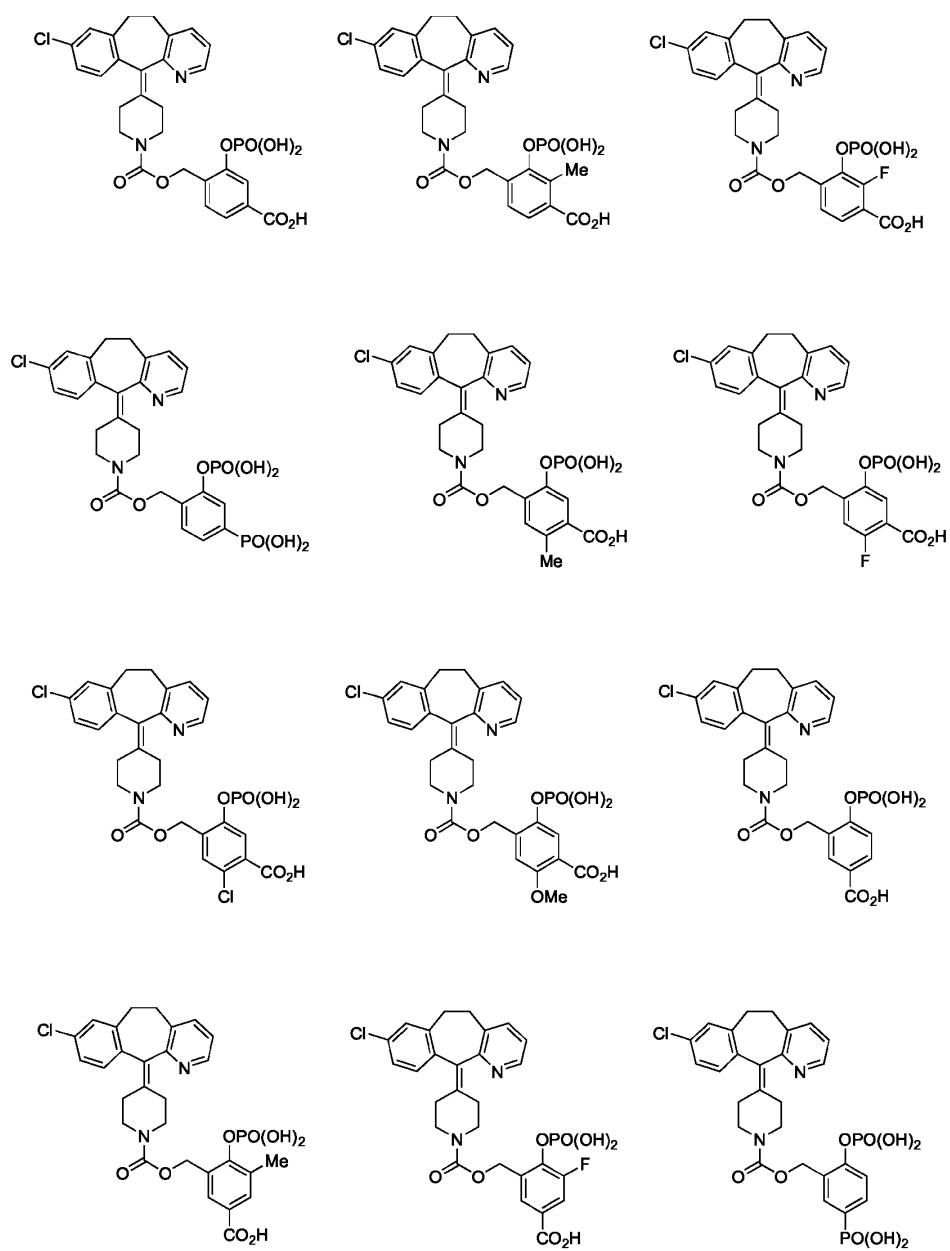


FIG. 28

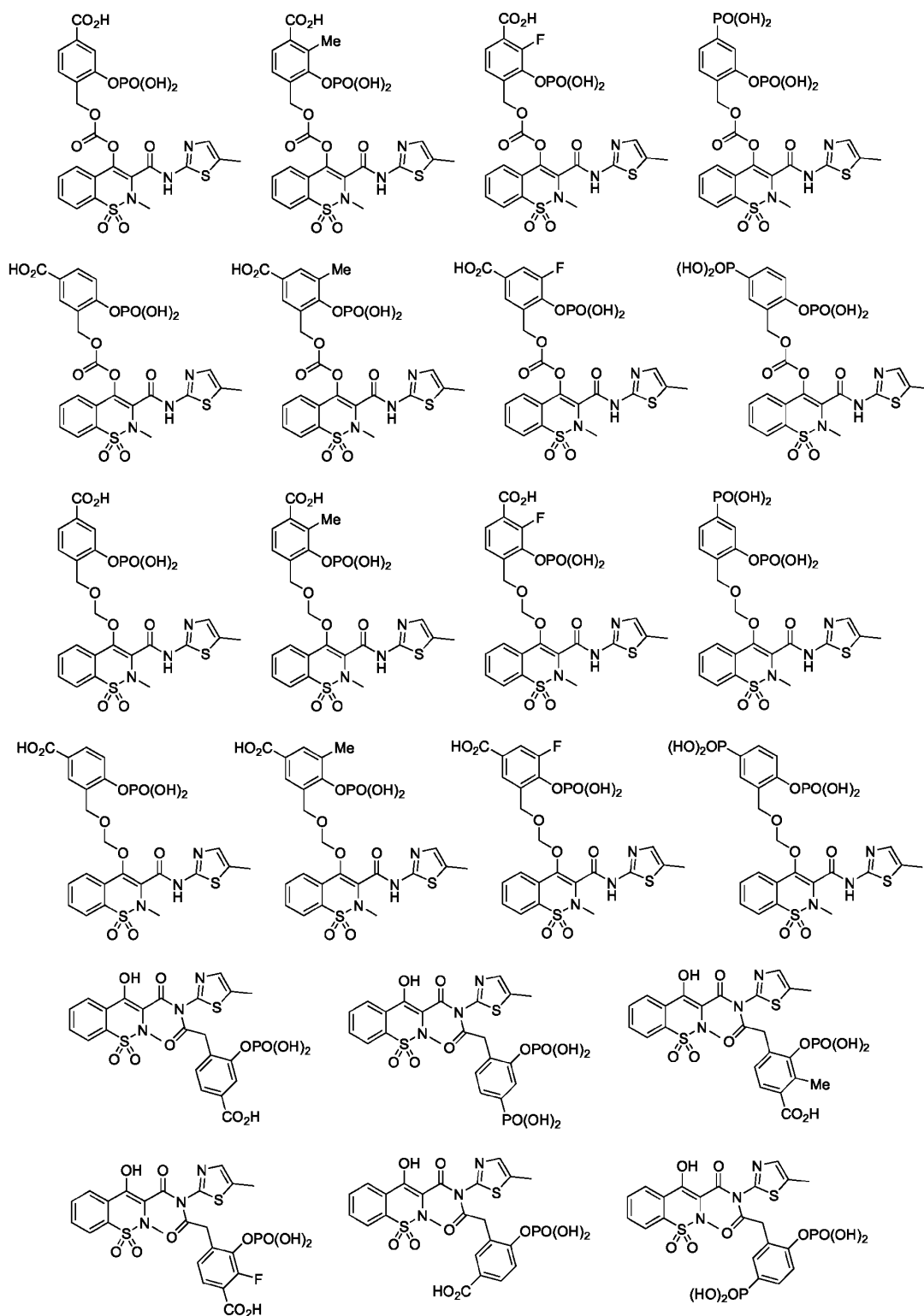


FIG. 29
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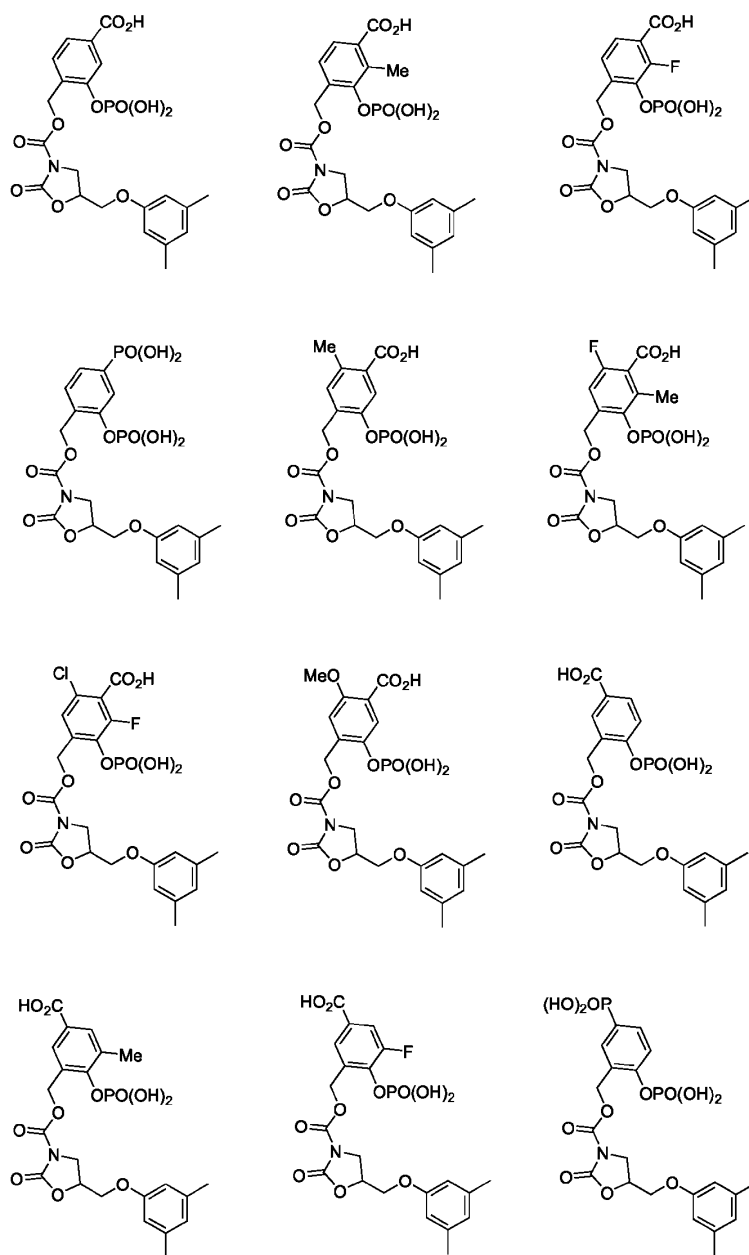


FIG. 30

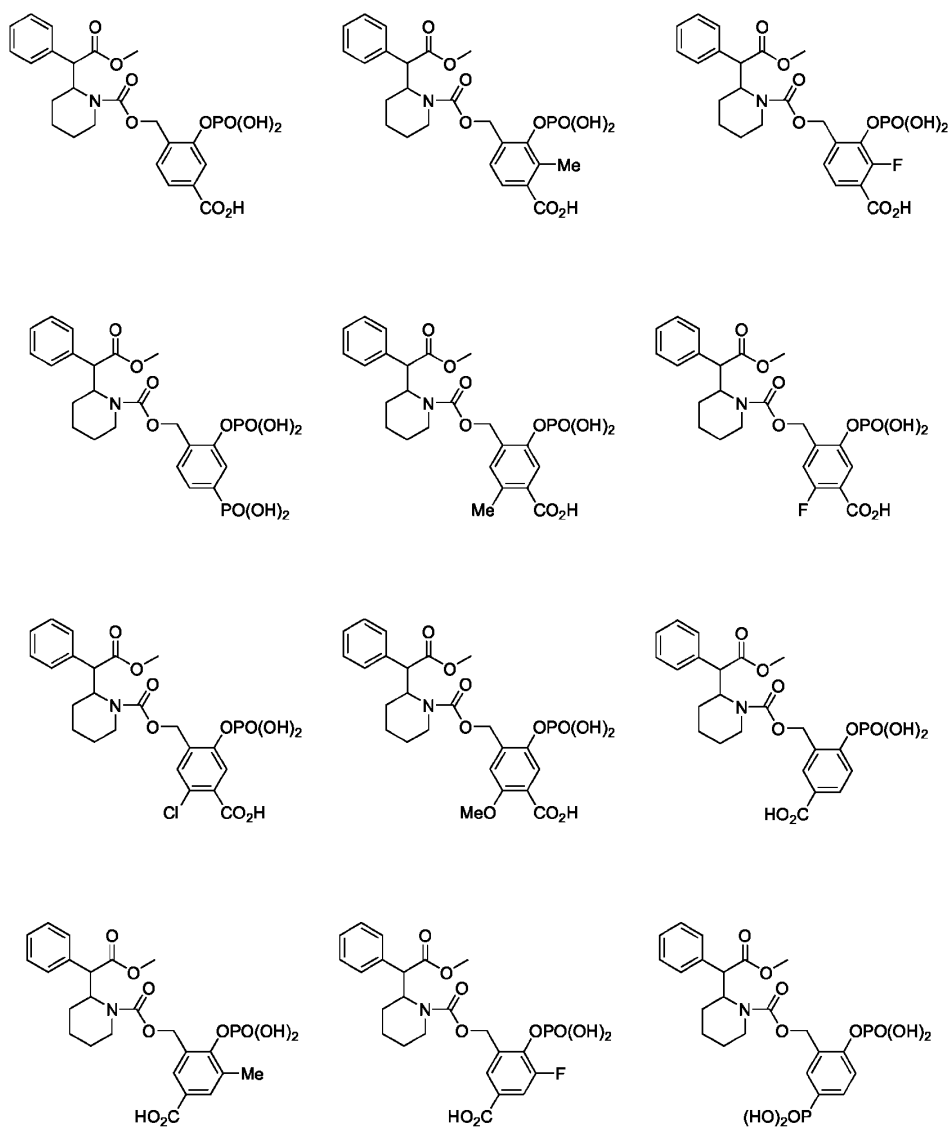


FIG. 31

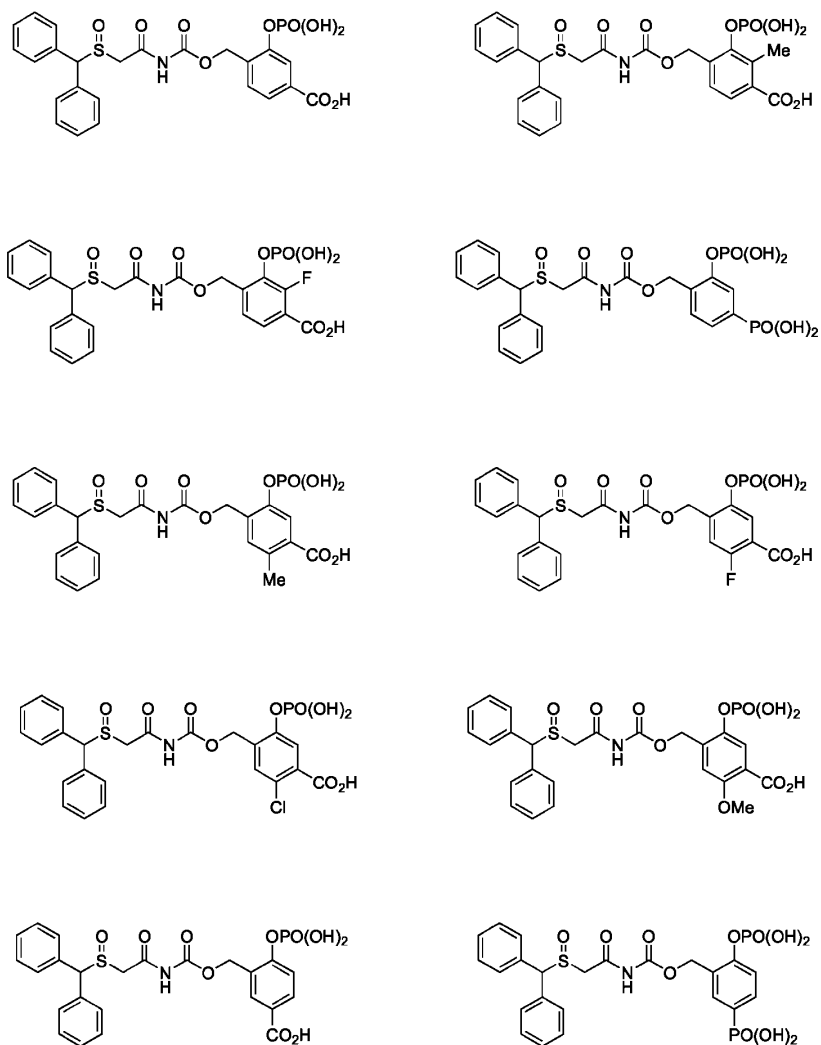
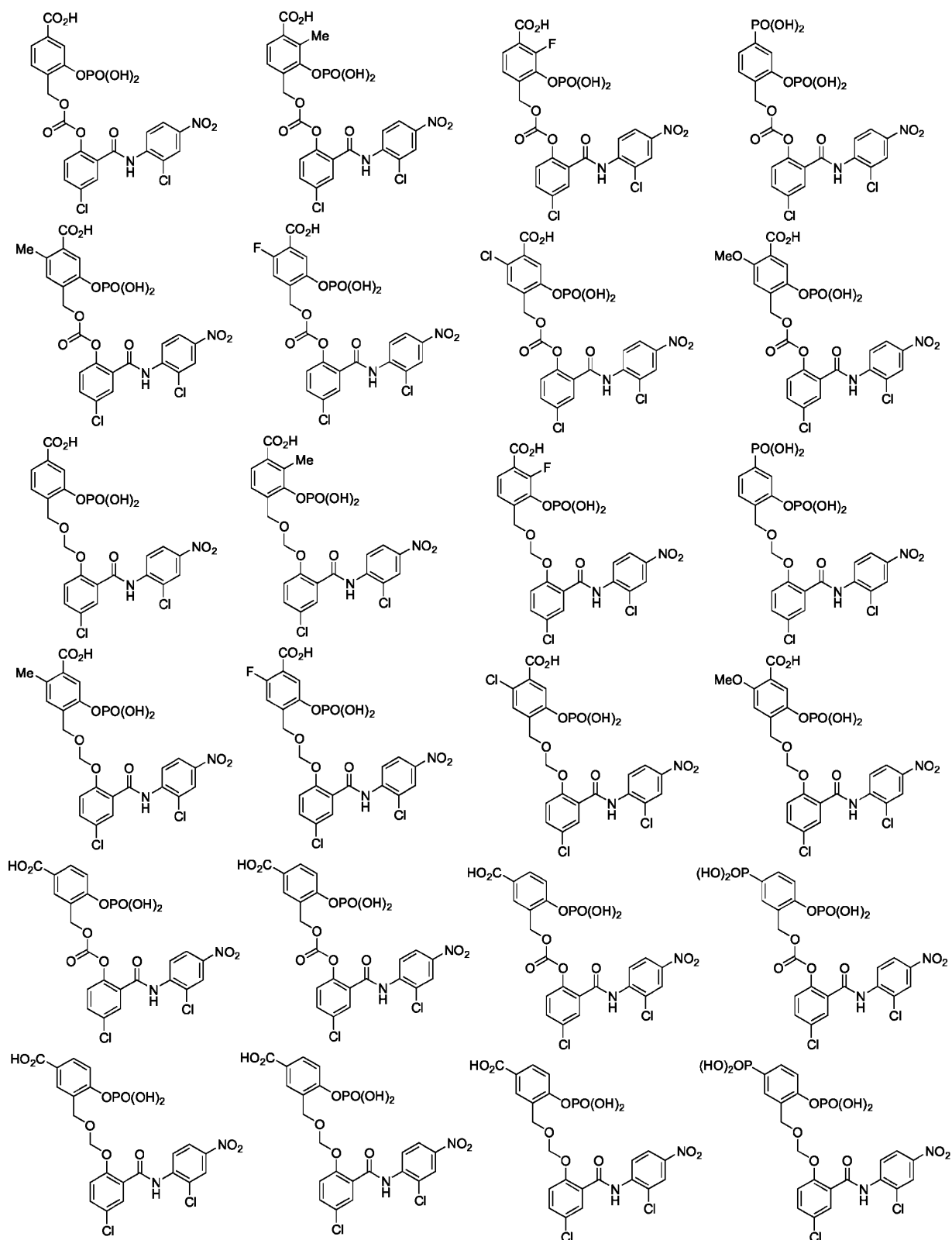


FIG. 32



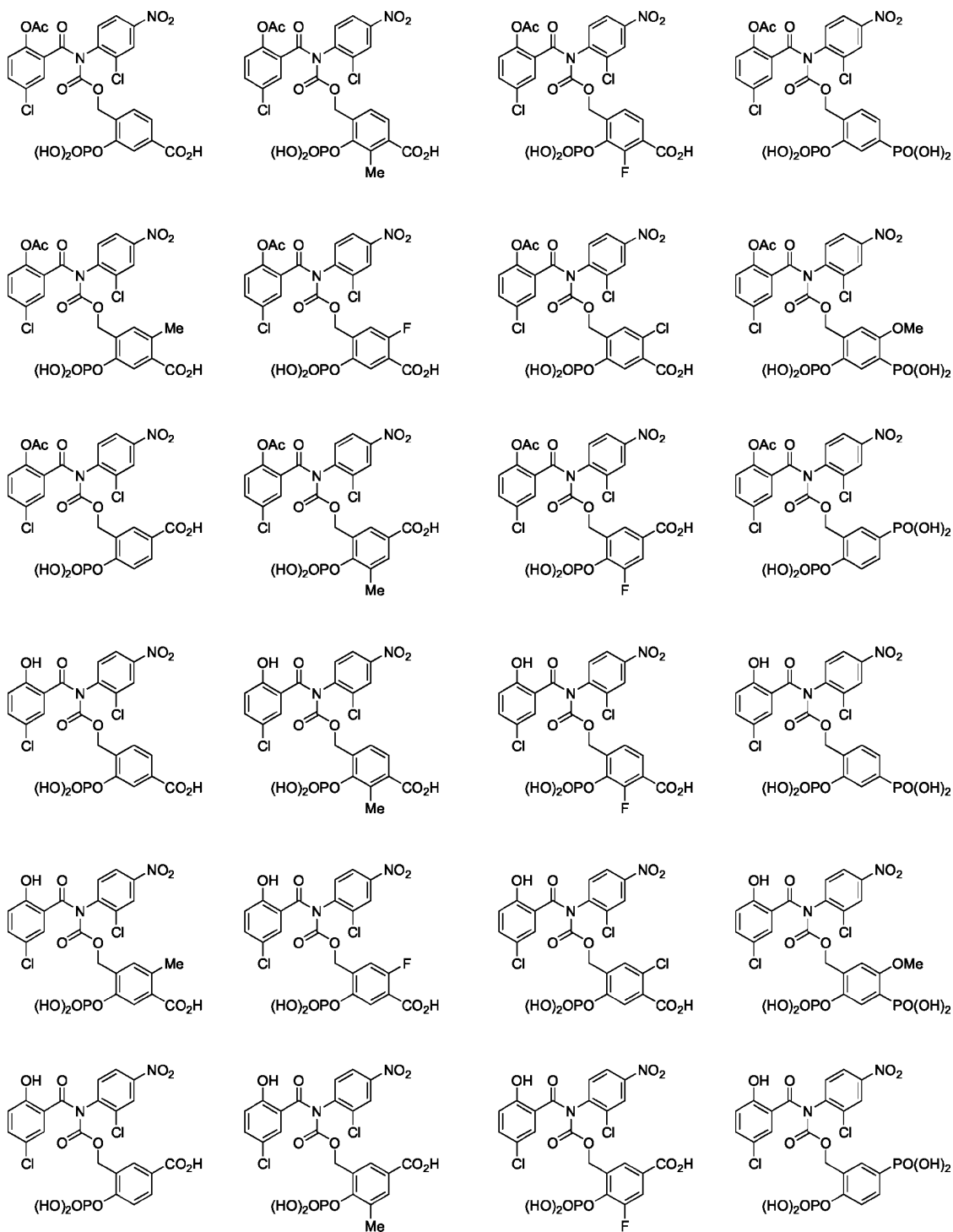


FIG. 33B
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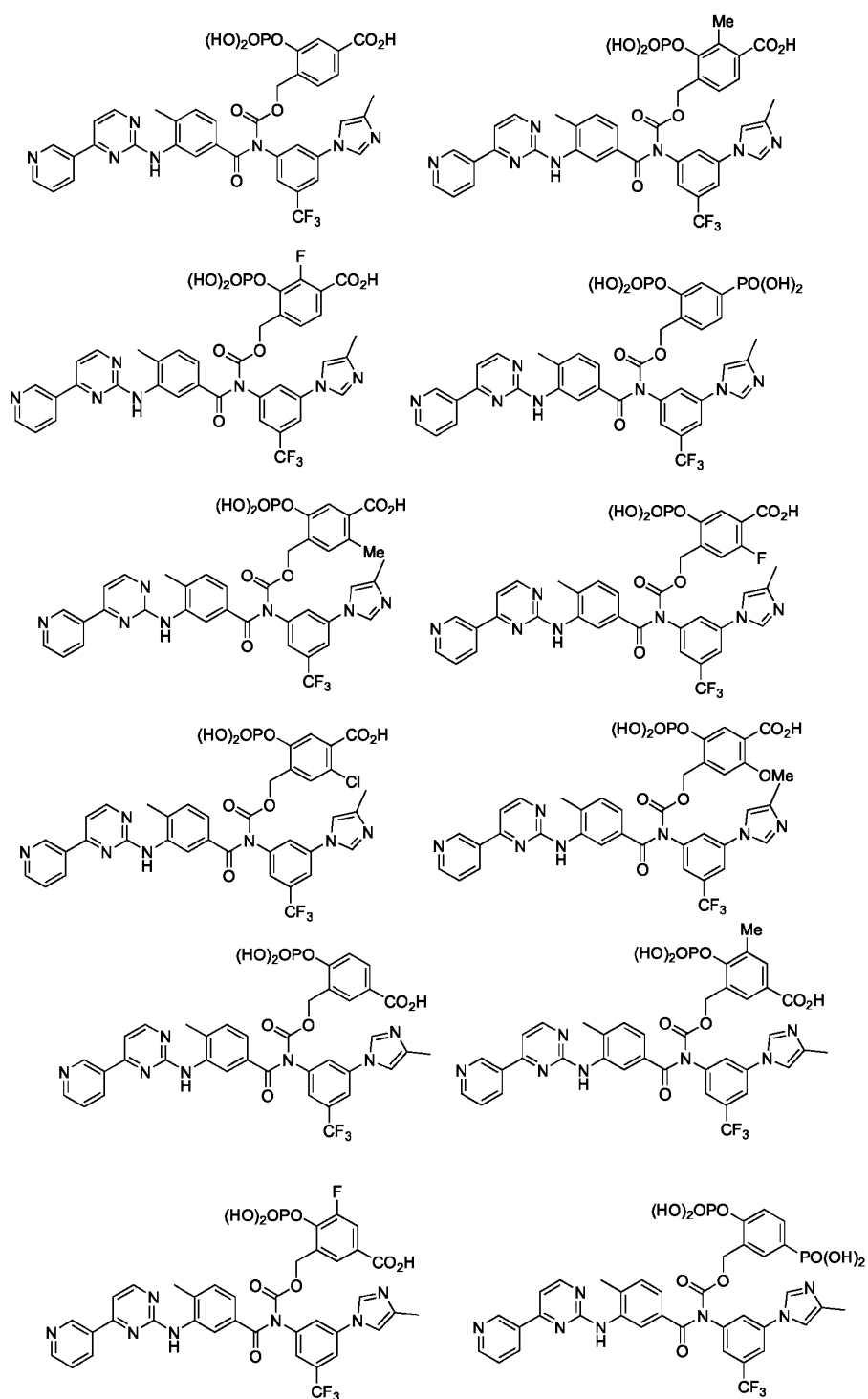


FIG. 34A

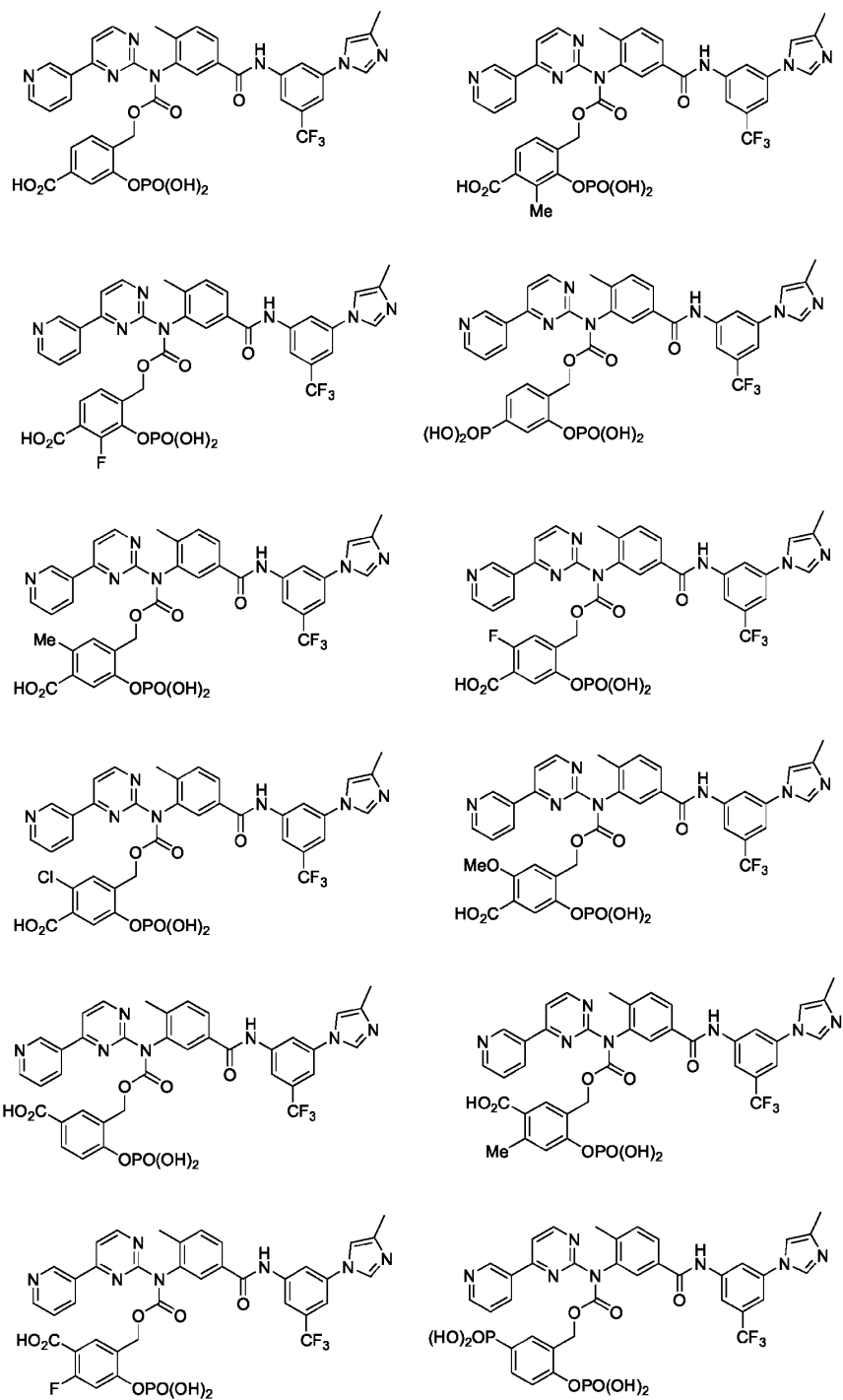


FIG. 34B

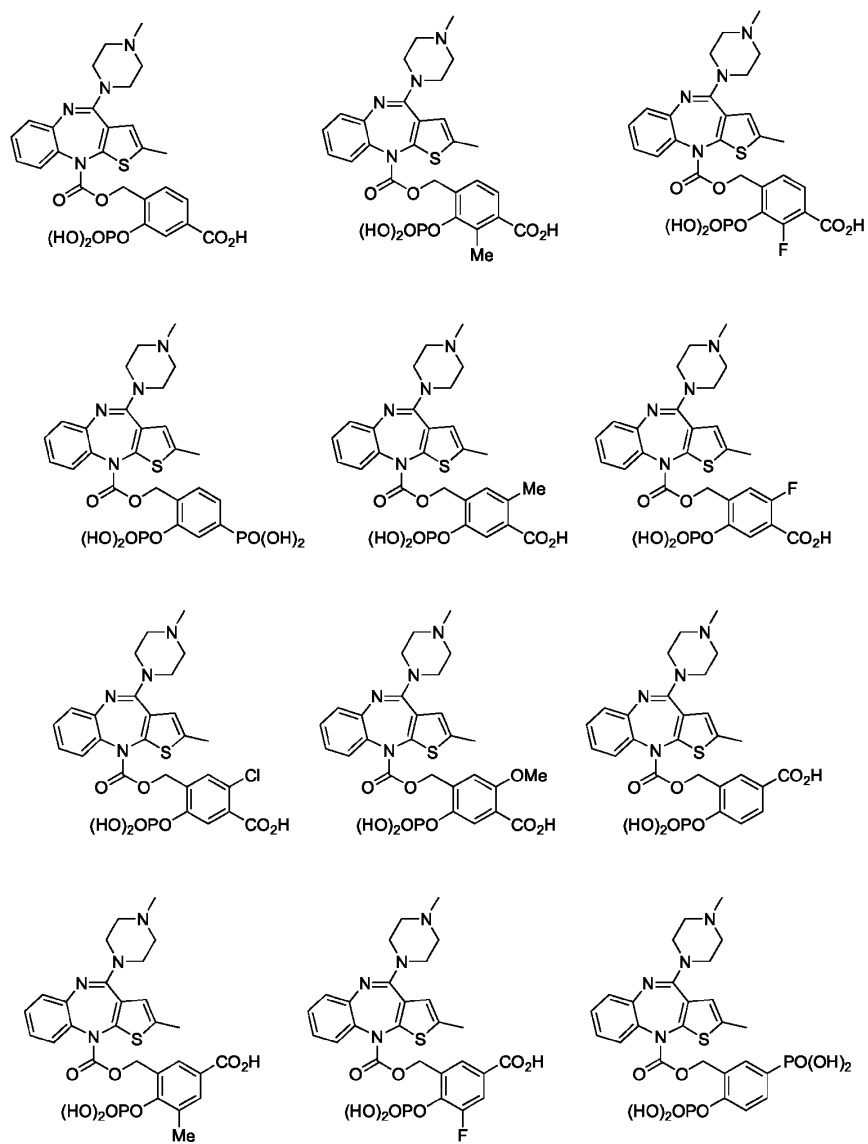


FIG. 35

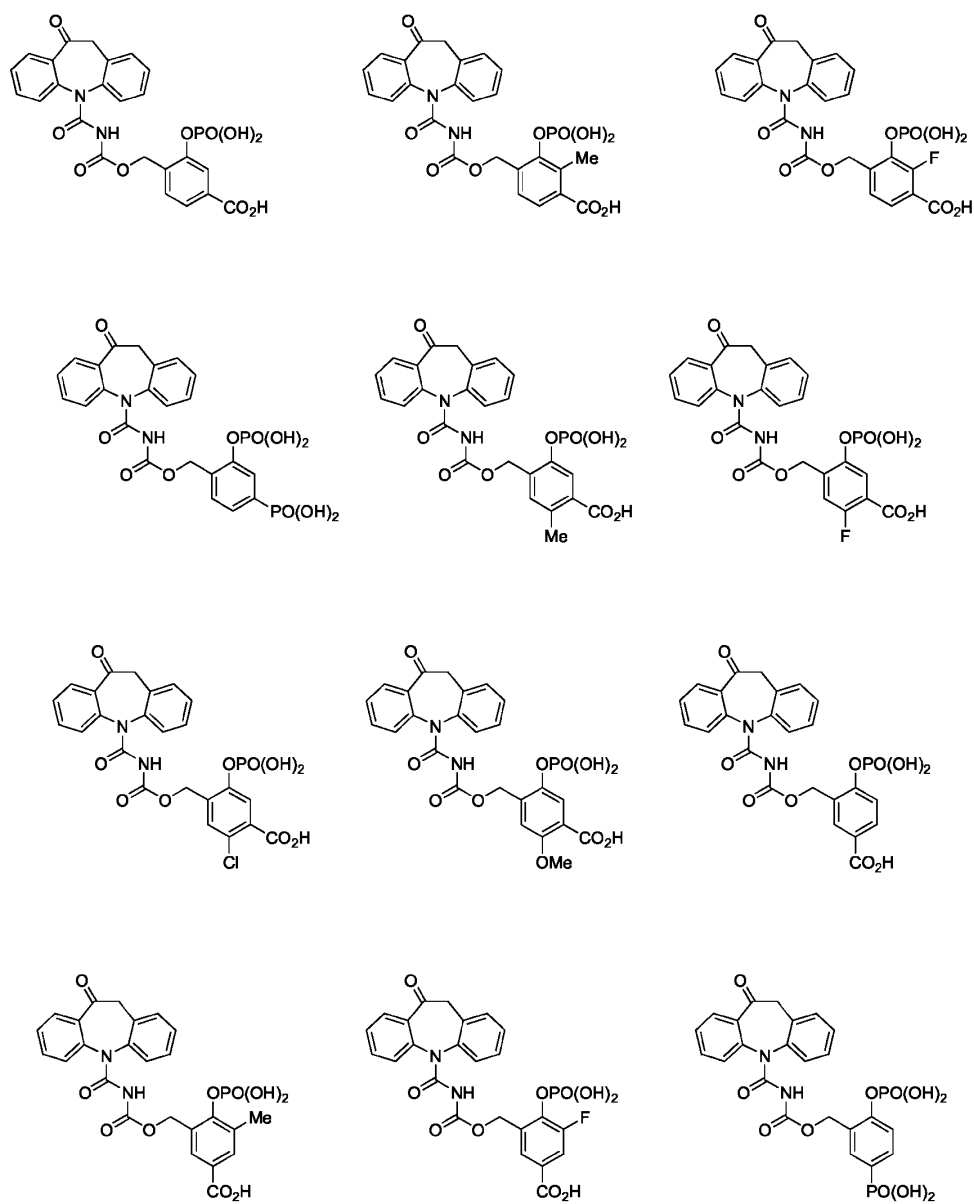


FIG. 36

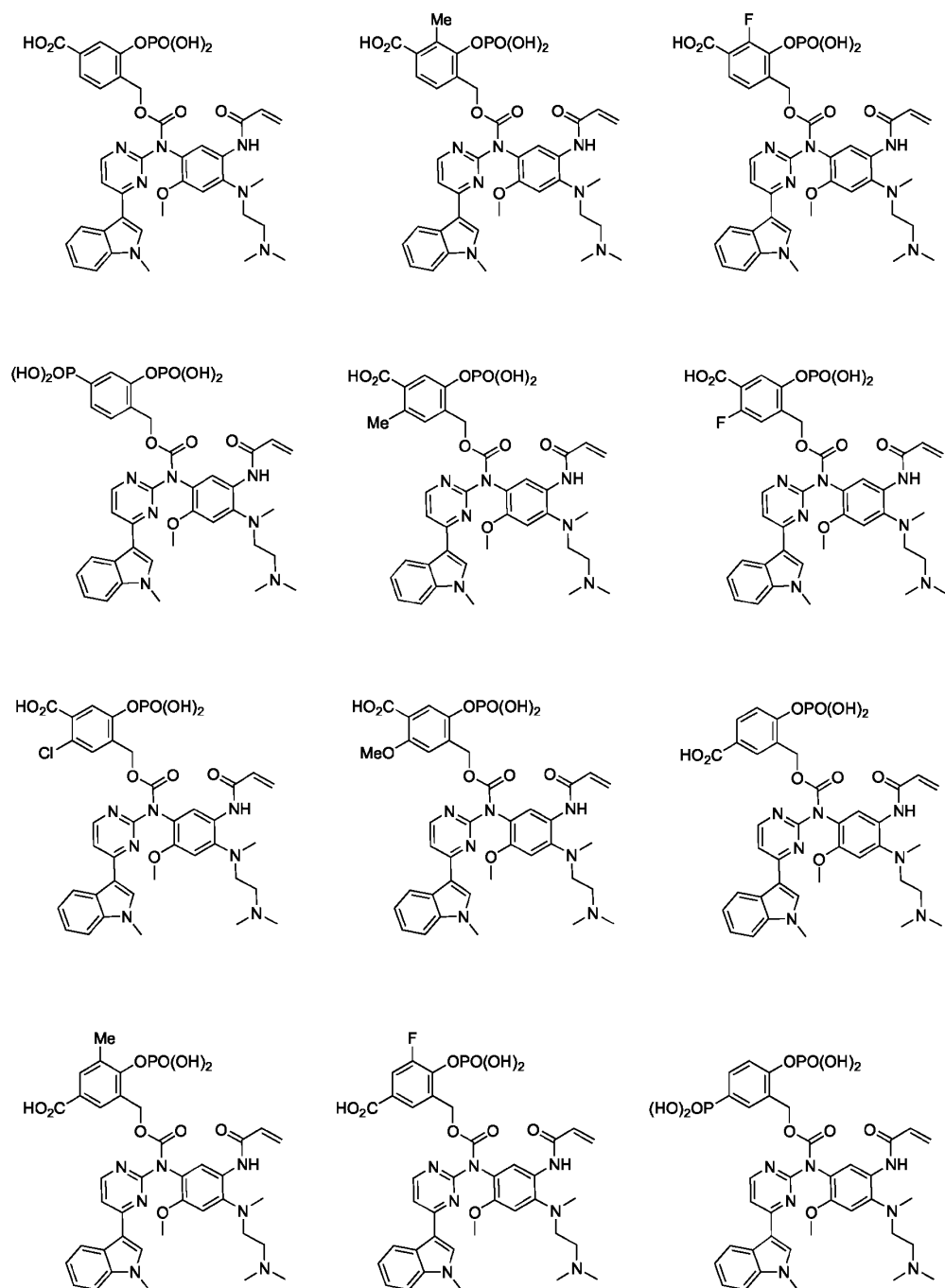


FIG. 37

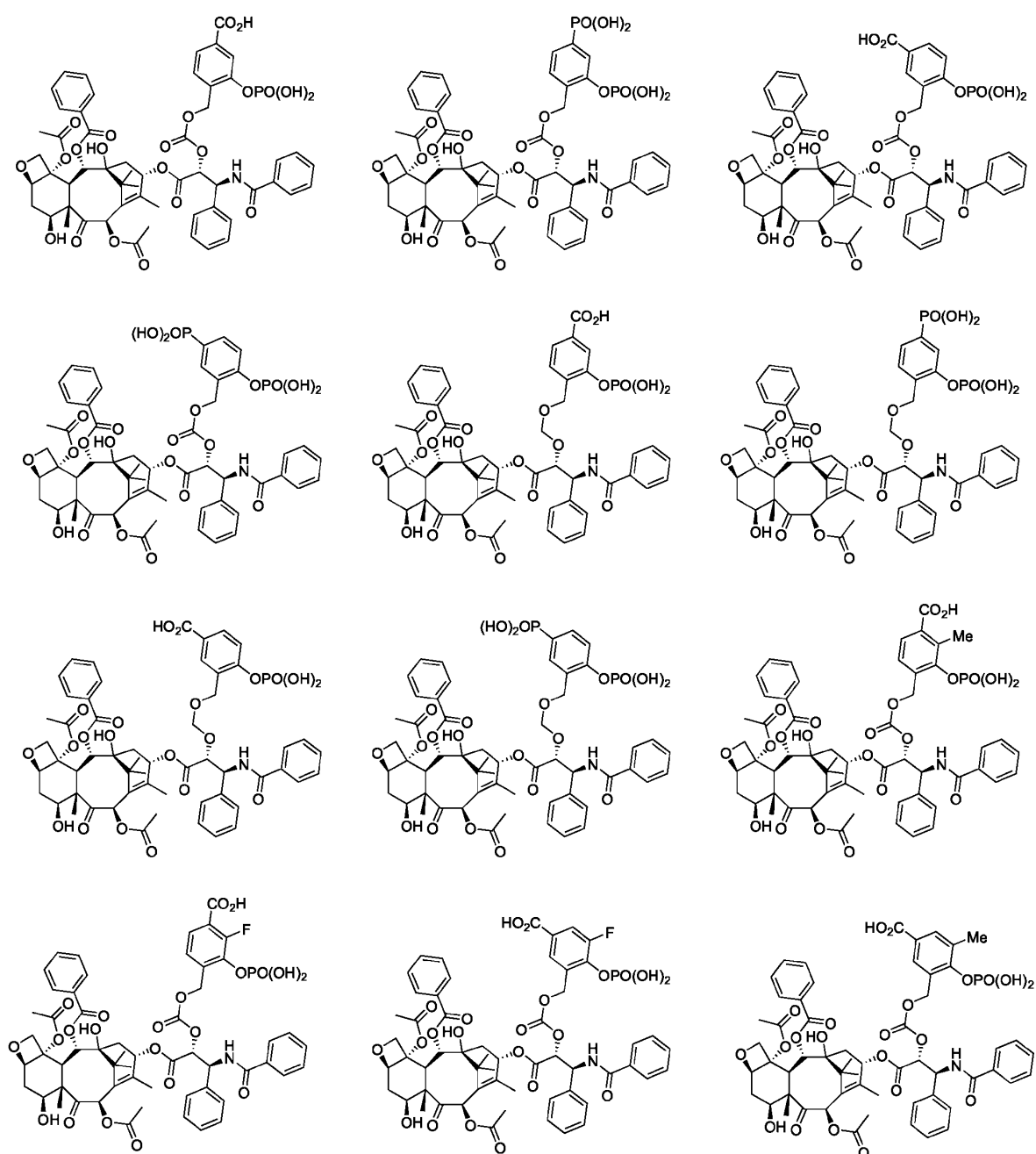


FIG. 38A

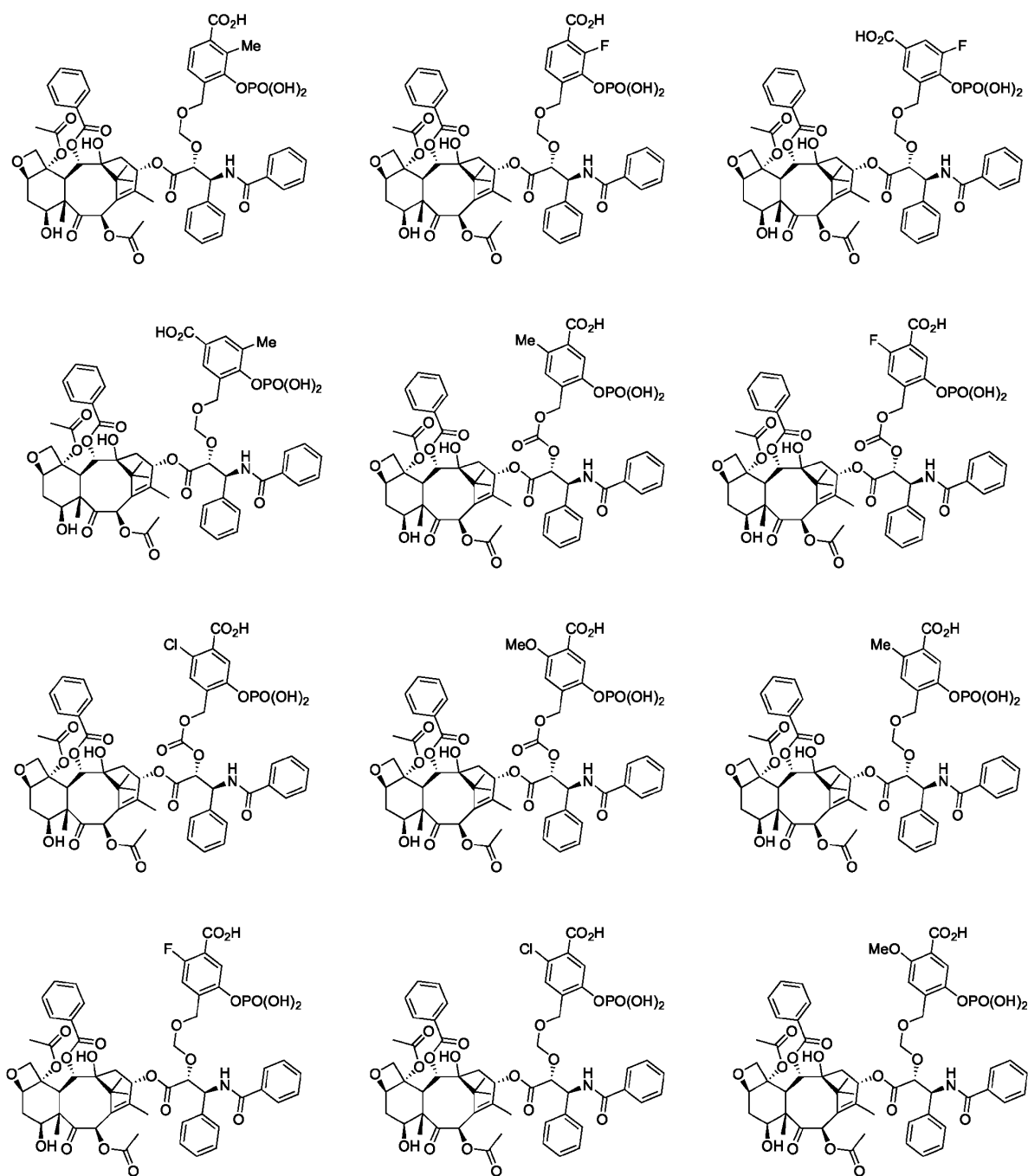


FIG. 38B

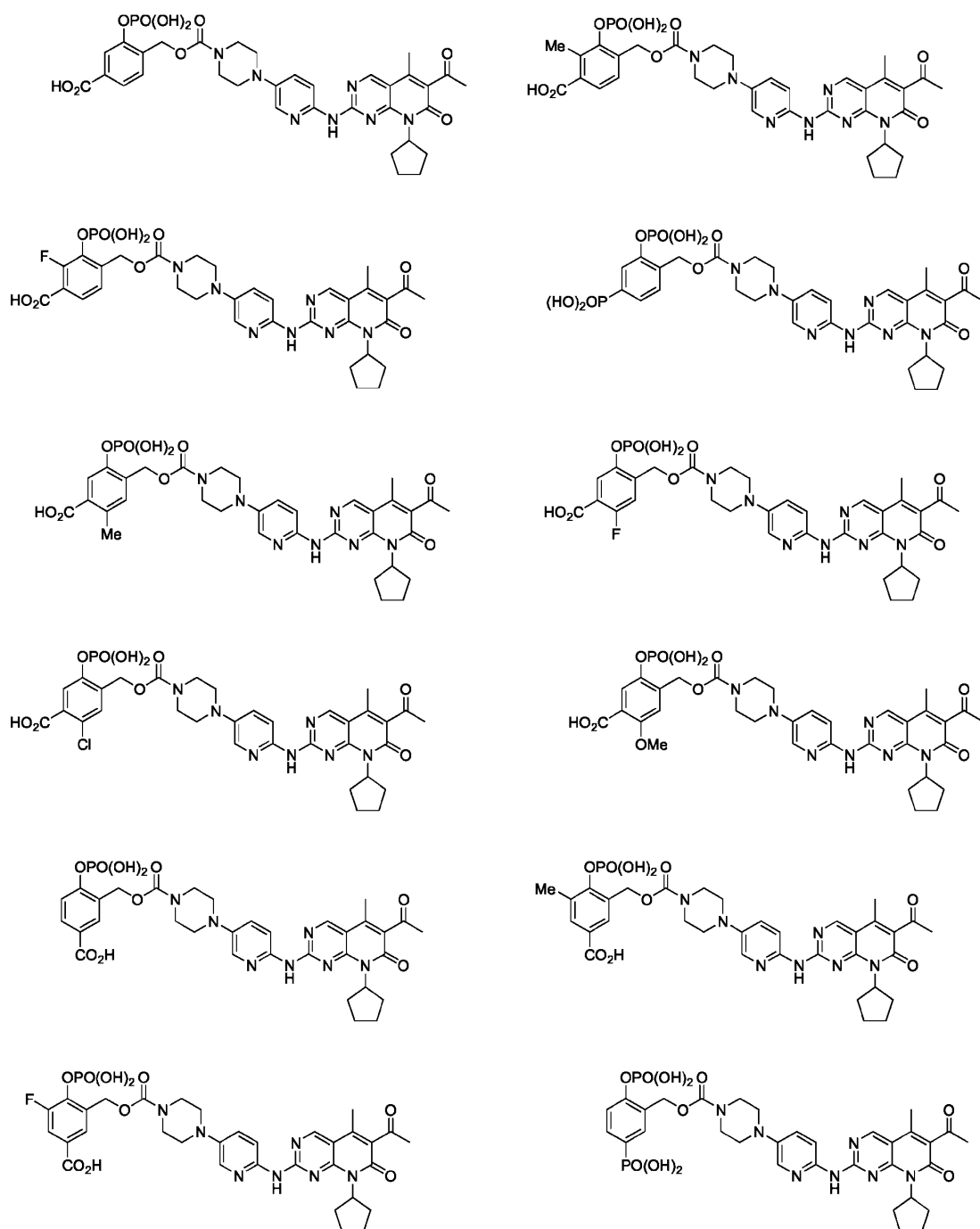


FIG. 39

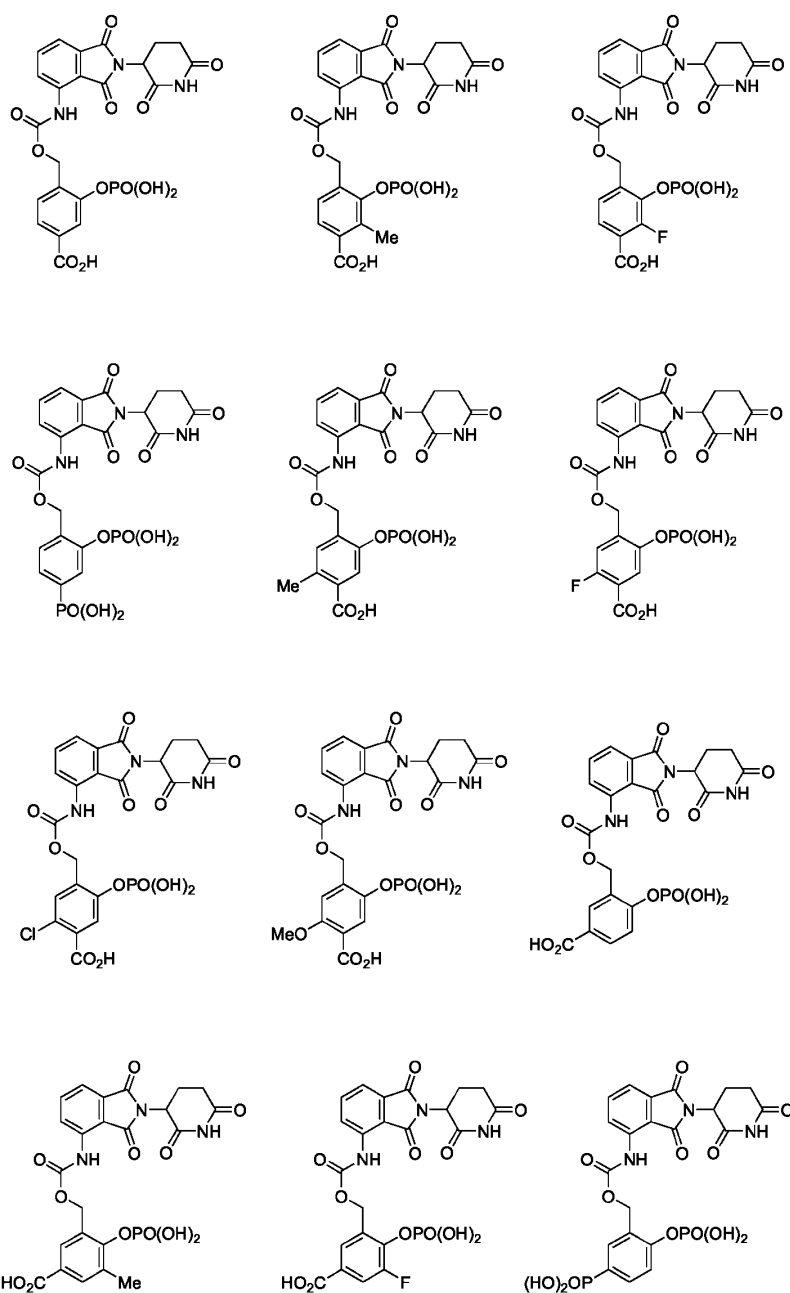


FIG. 40

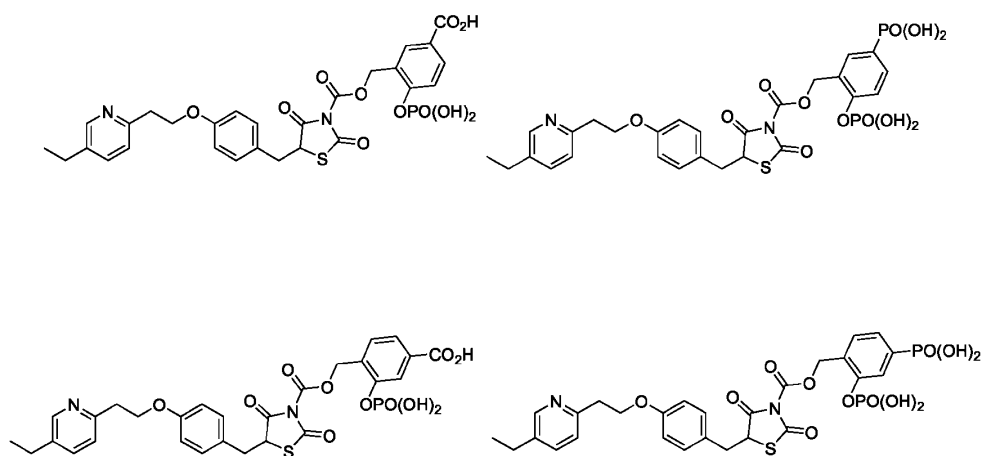


FIG. 41

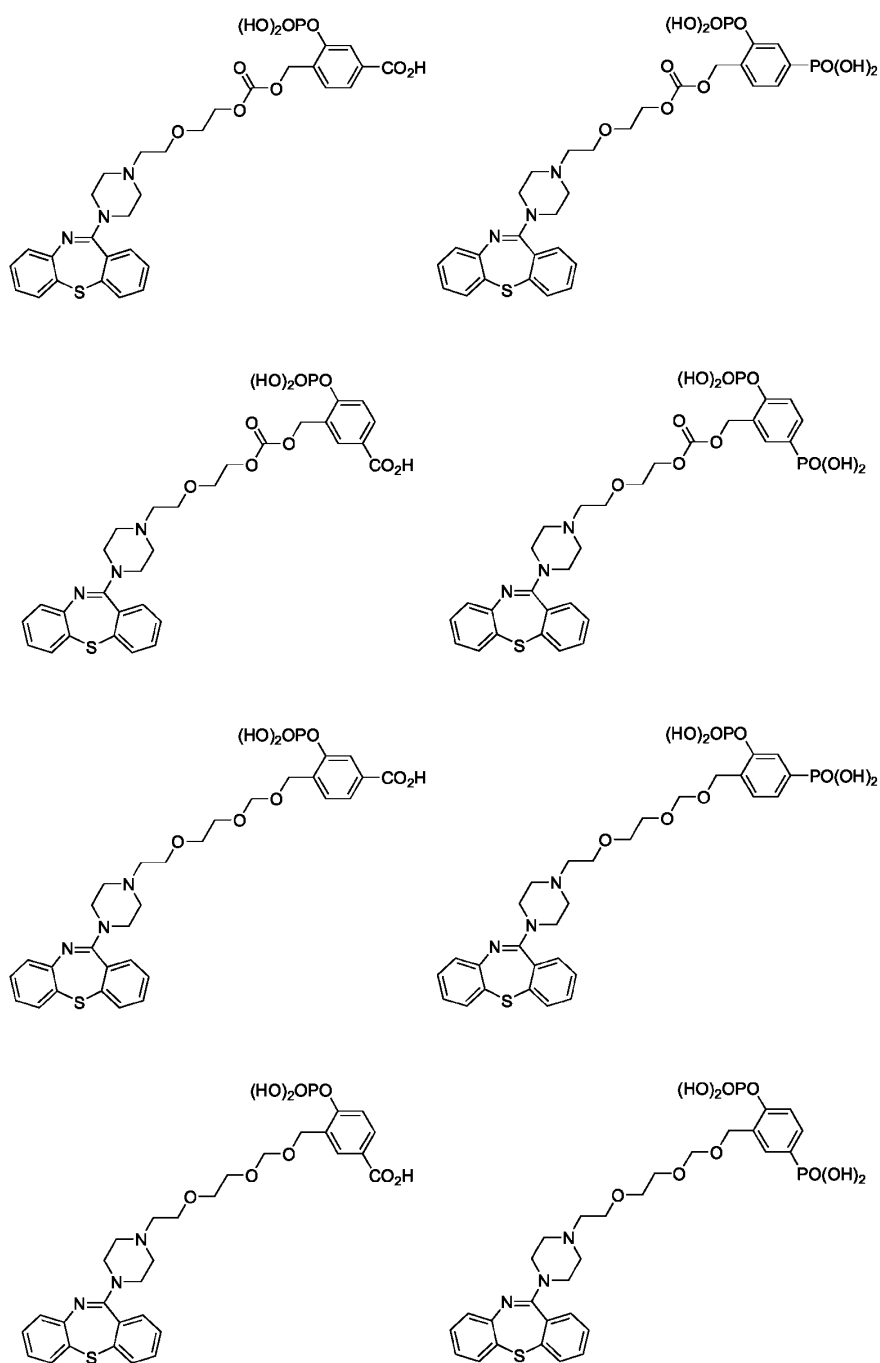


FIG. 42A

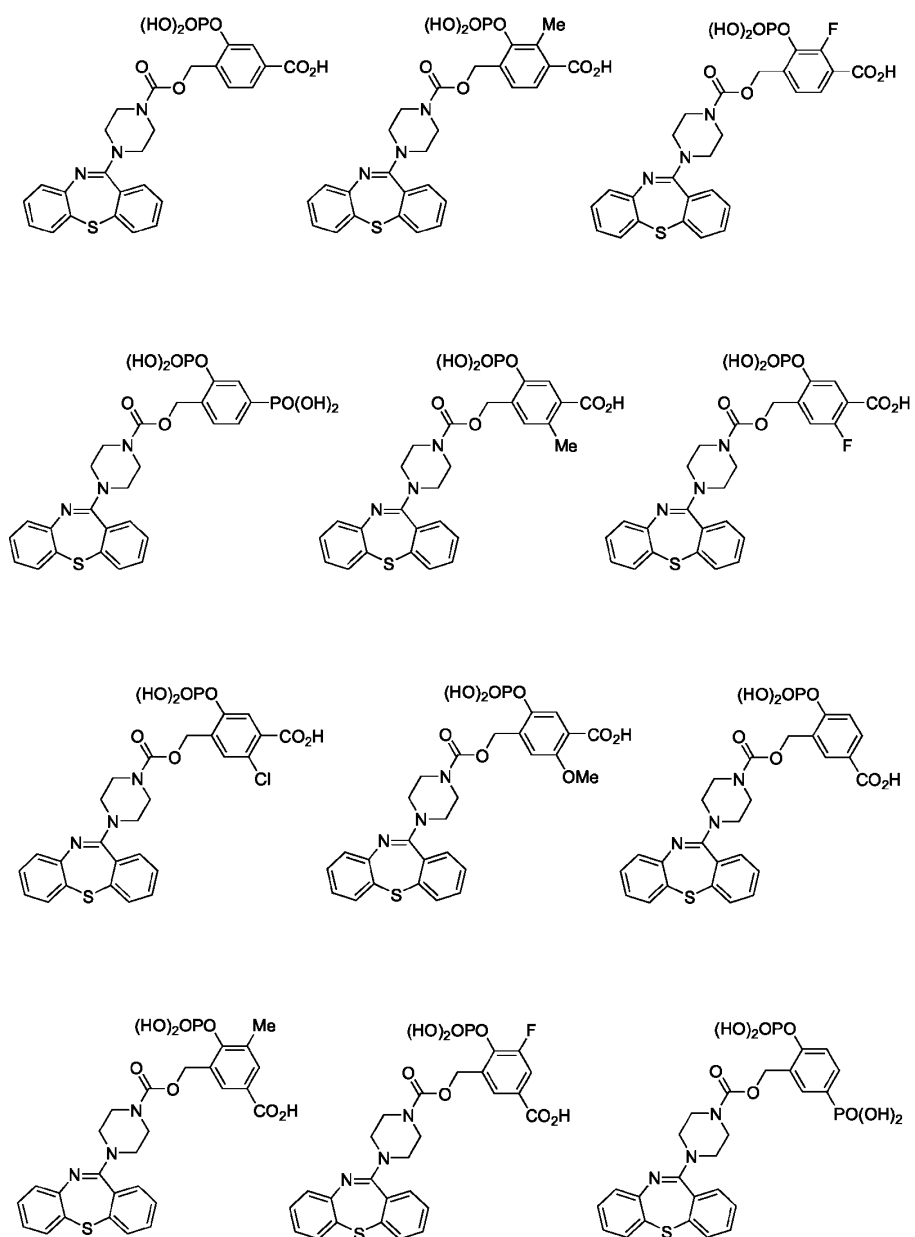


FIG. 42B

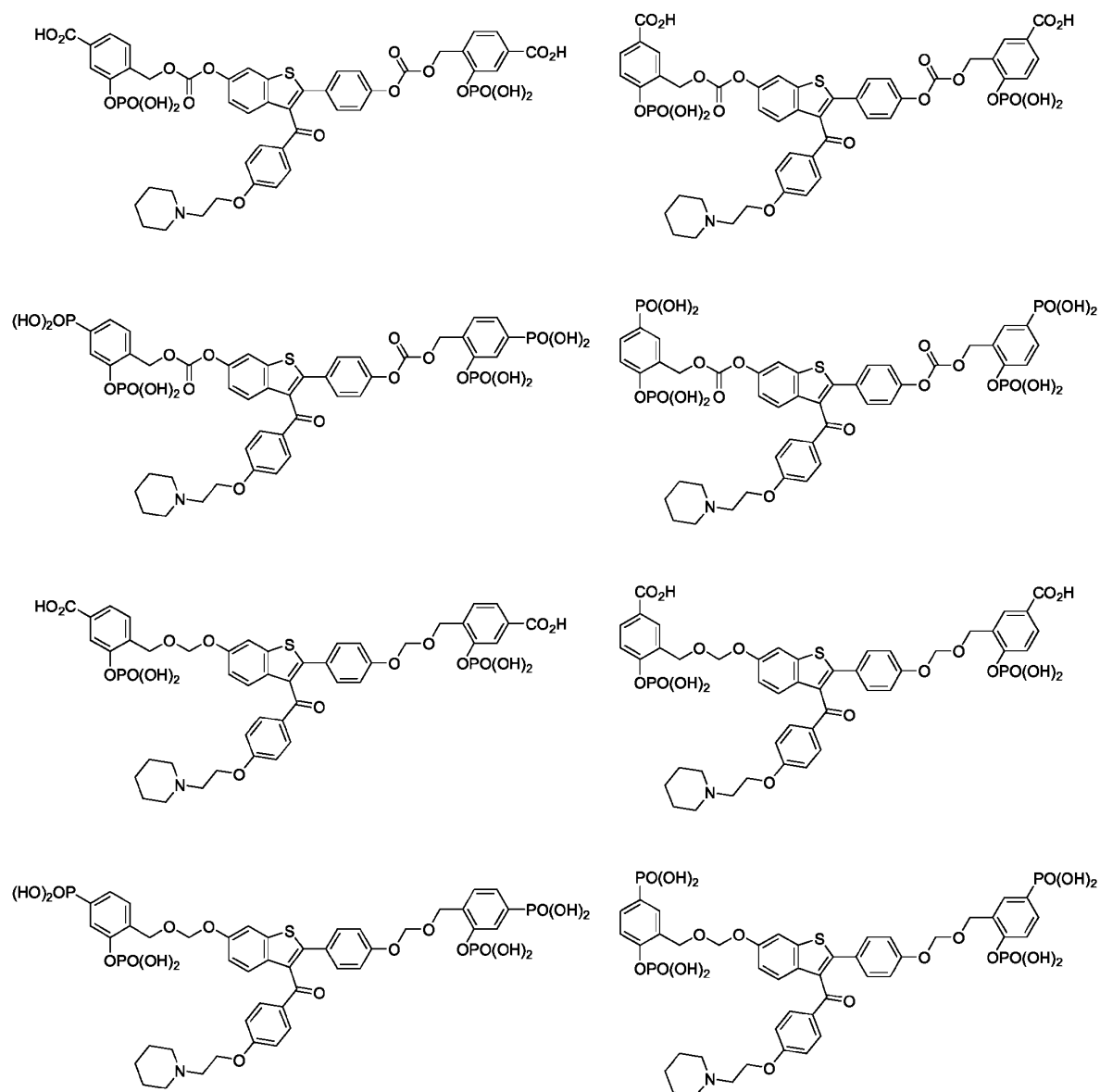


FIG. 43

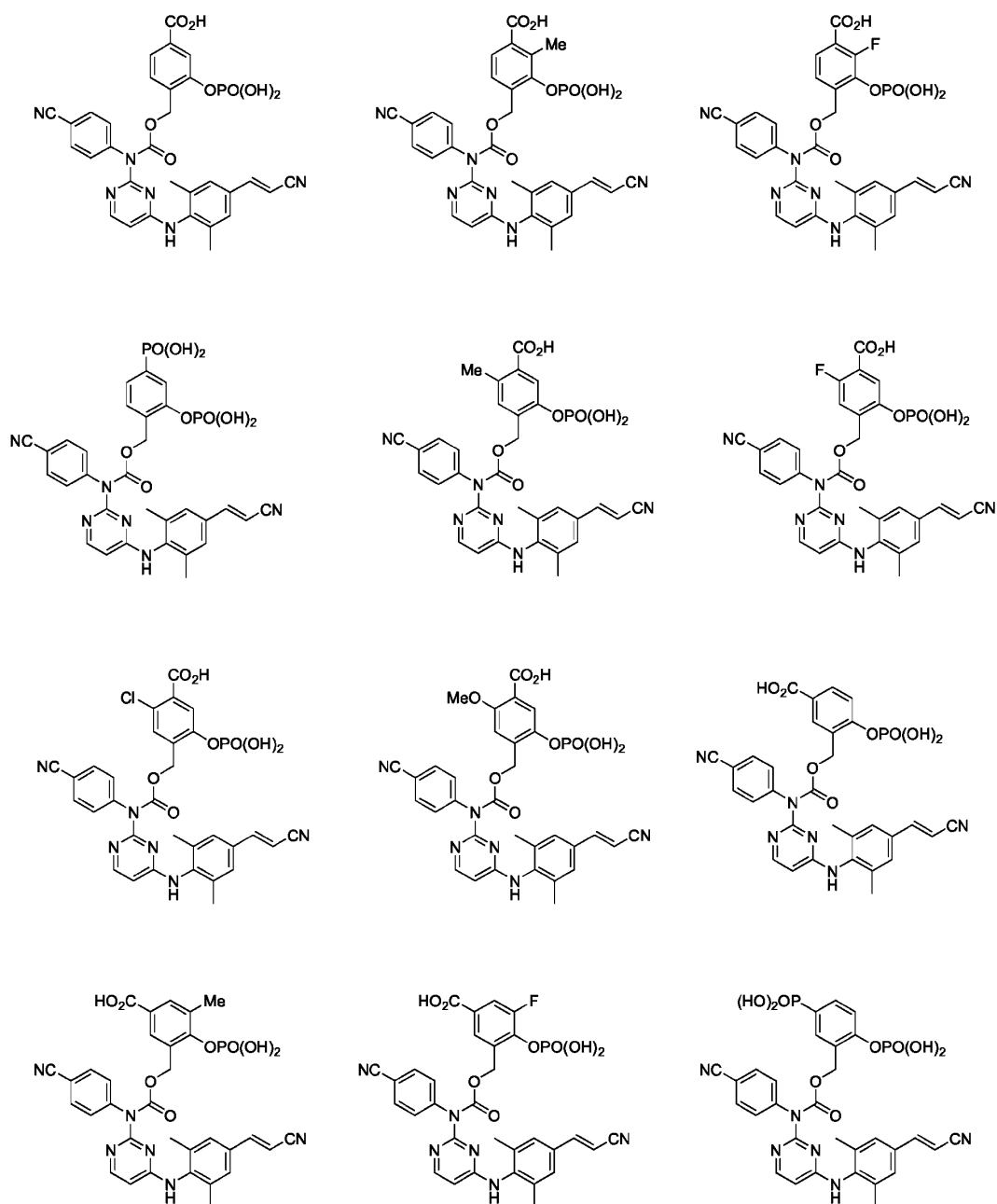


FIG. 44

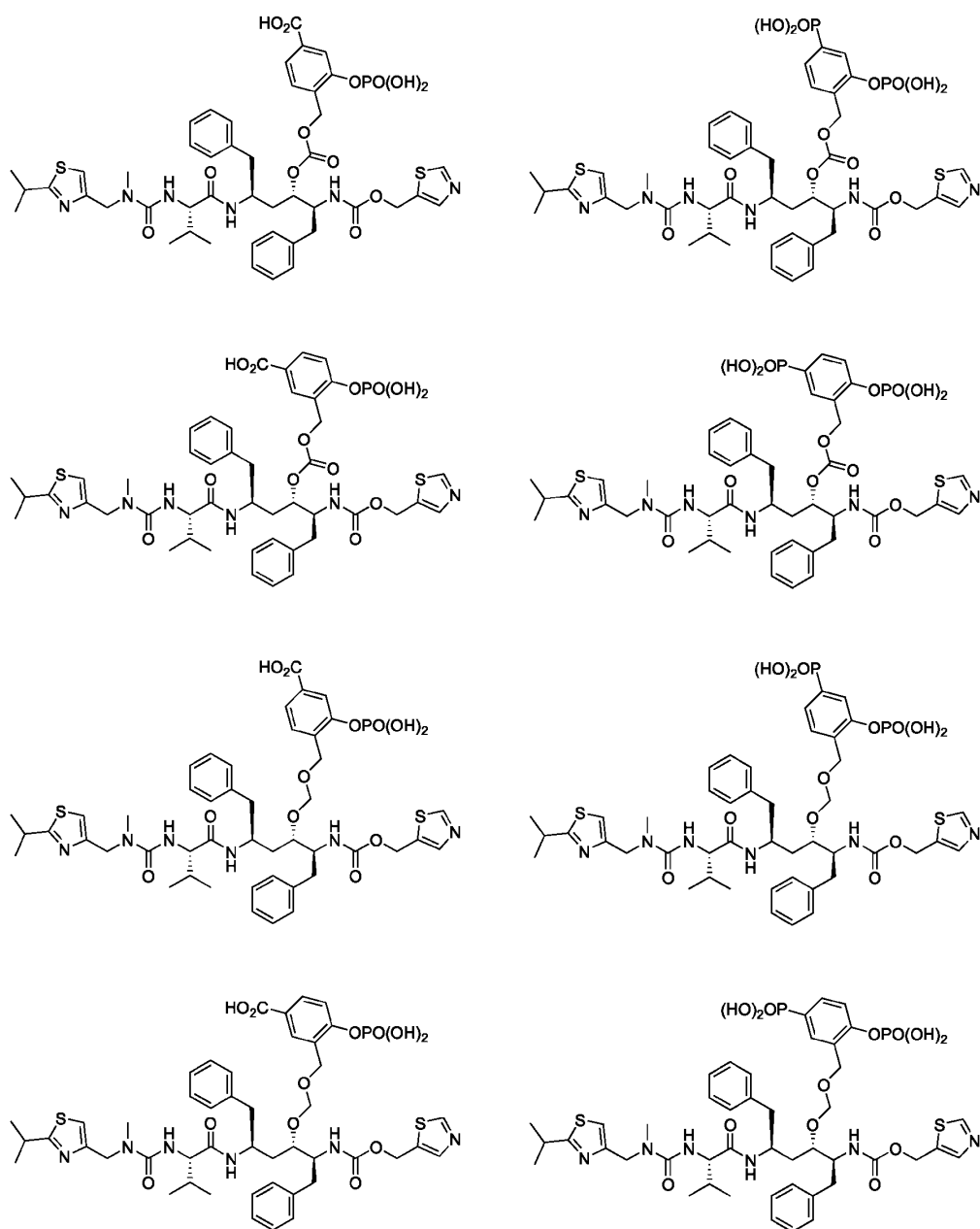


FIG. 45

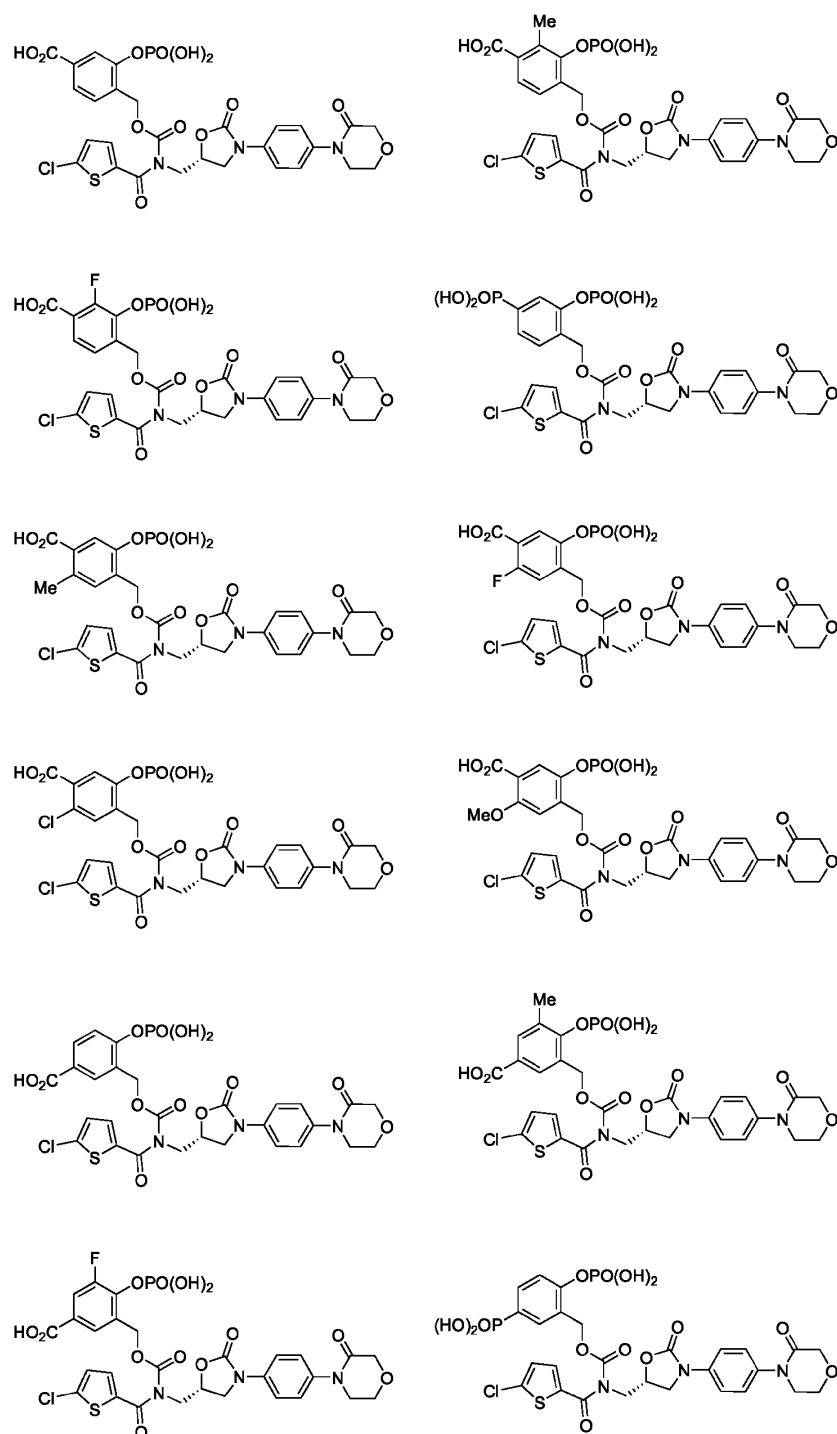
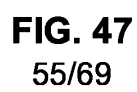


FIG. 46



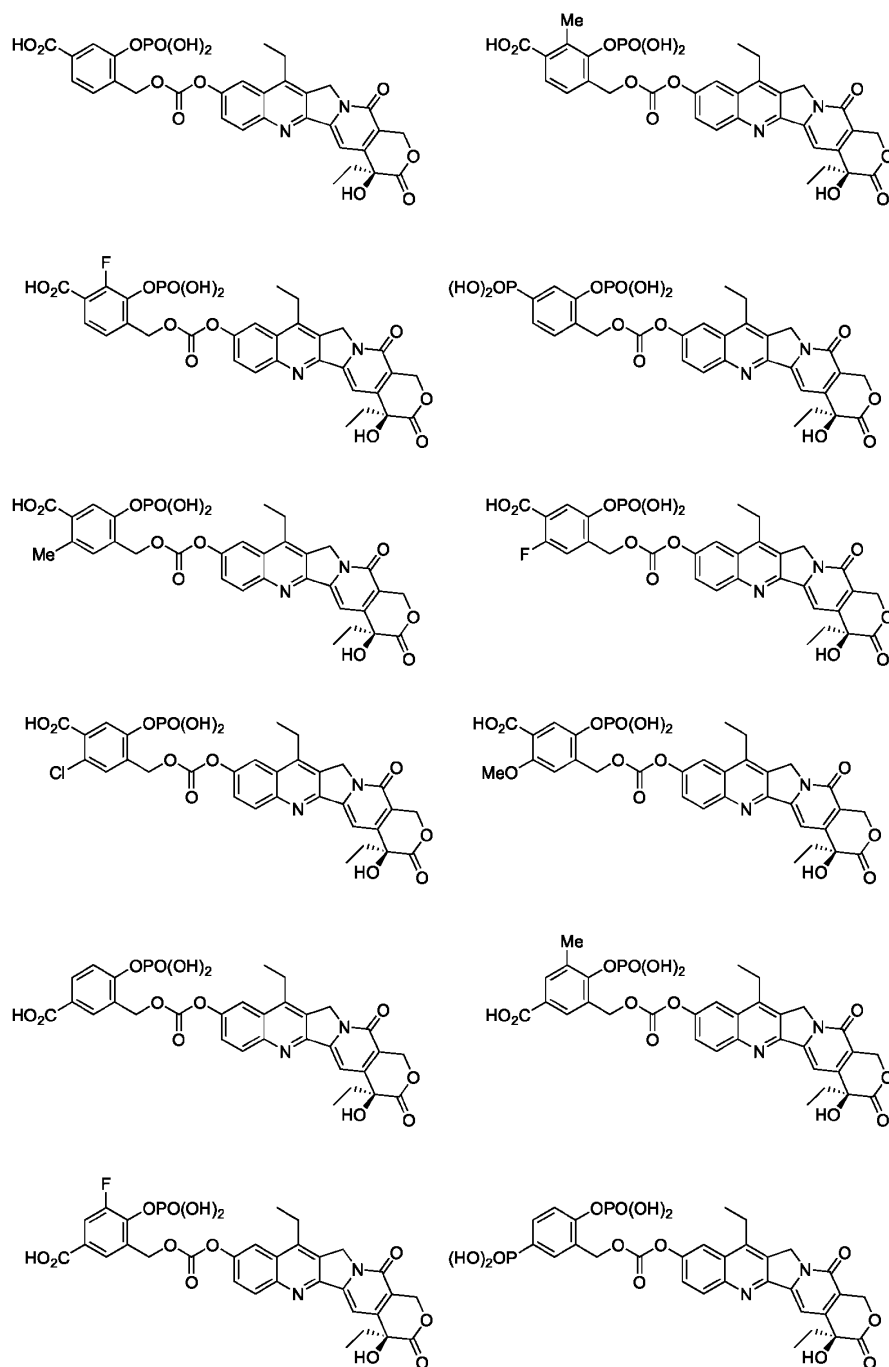


FIG. 48A

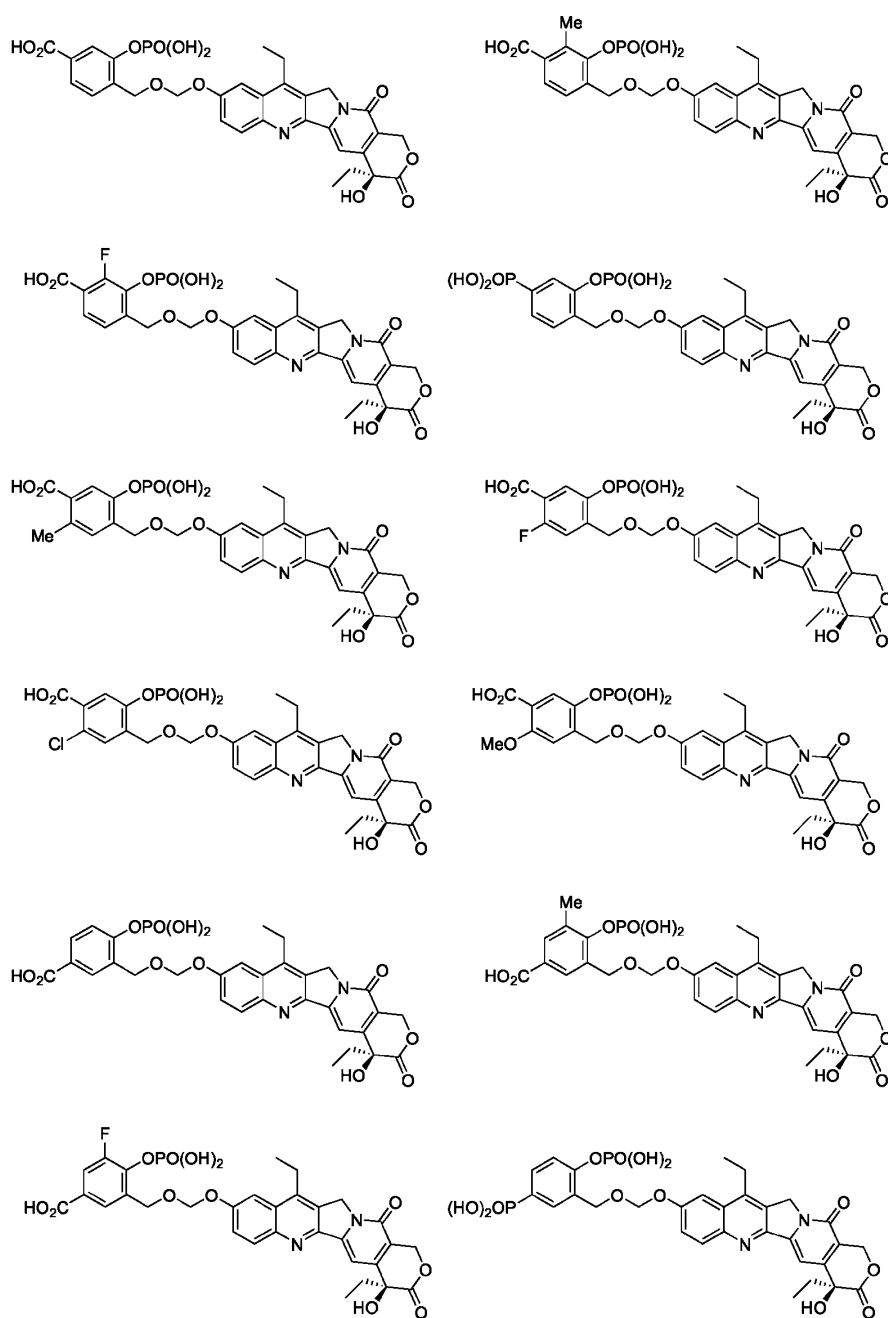


FIG. 48B

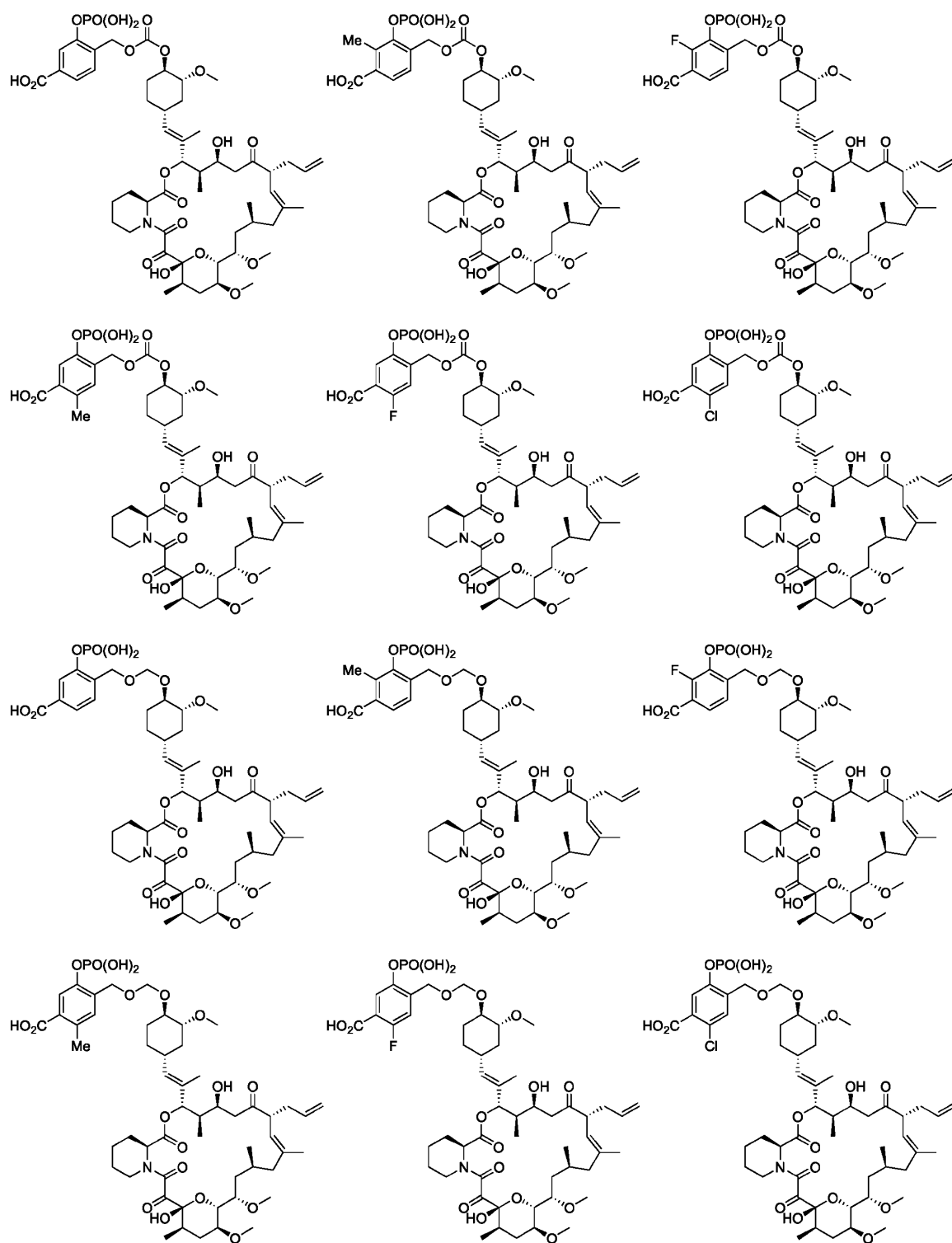


FIG. 49A
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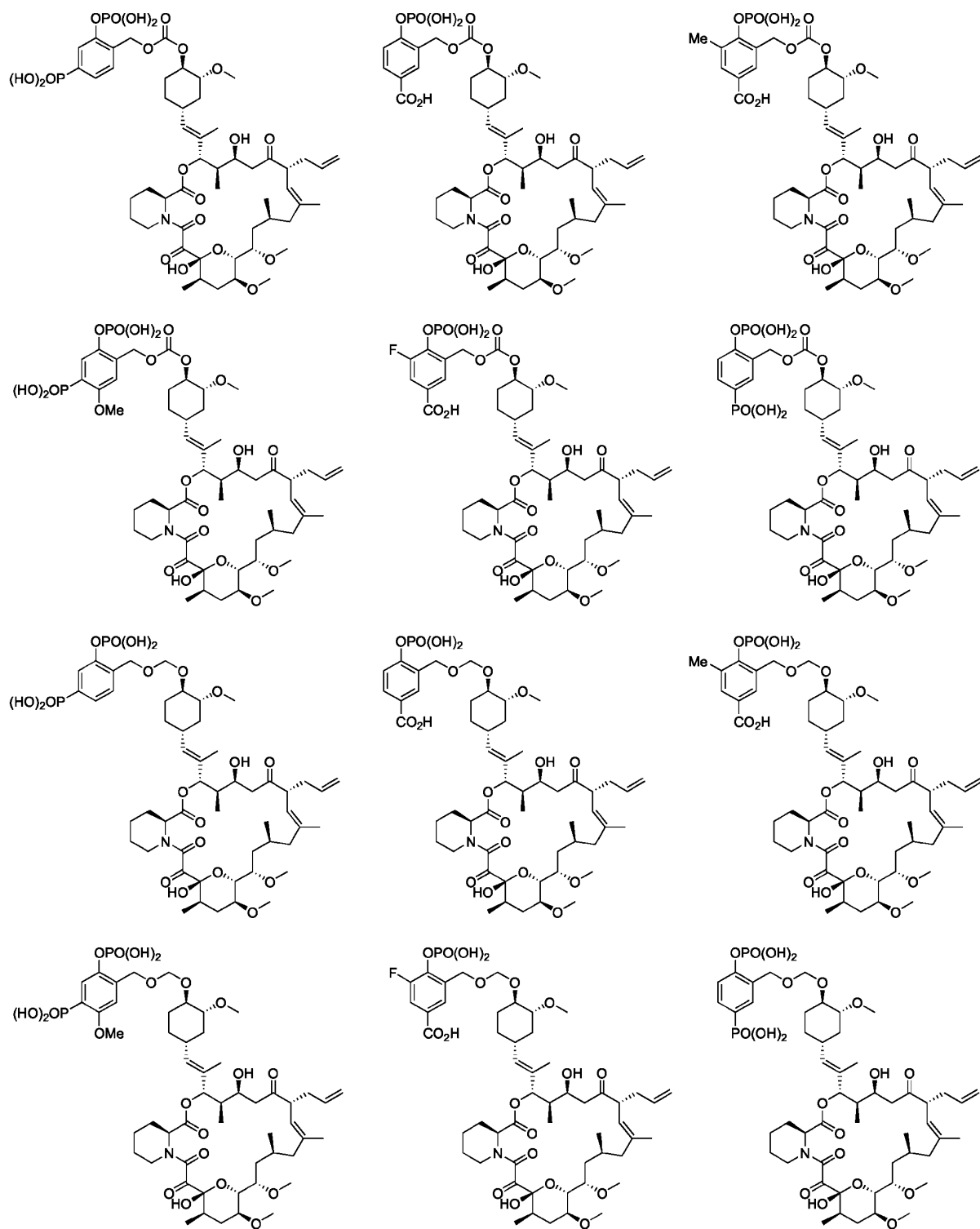


FIG. 49B
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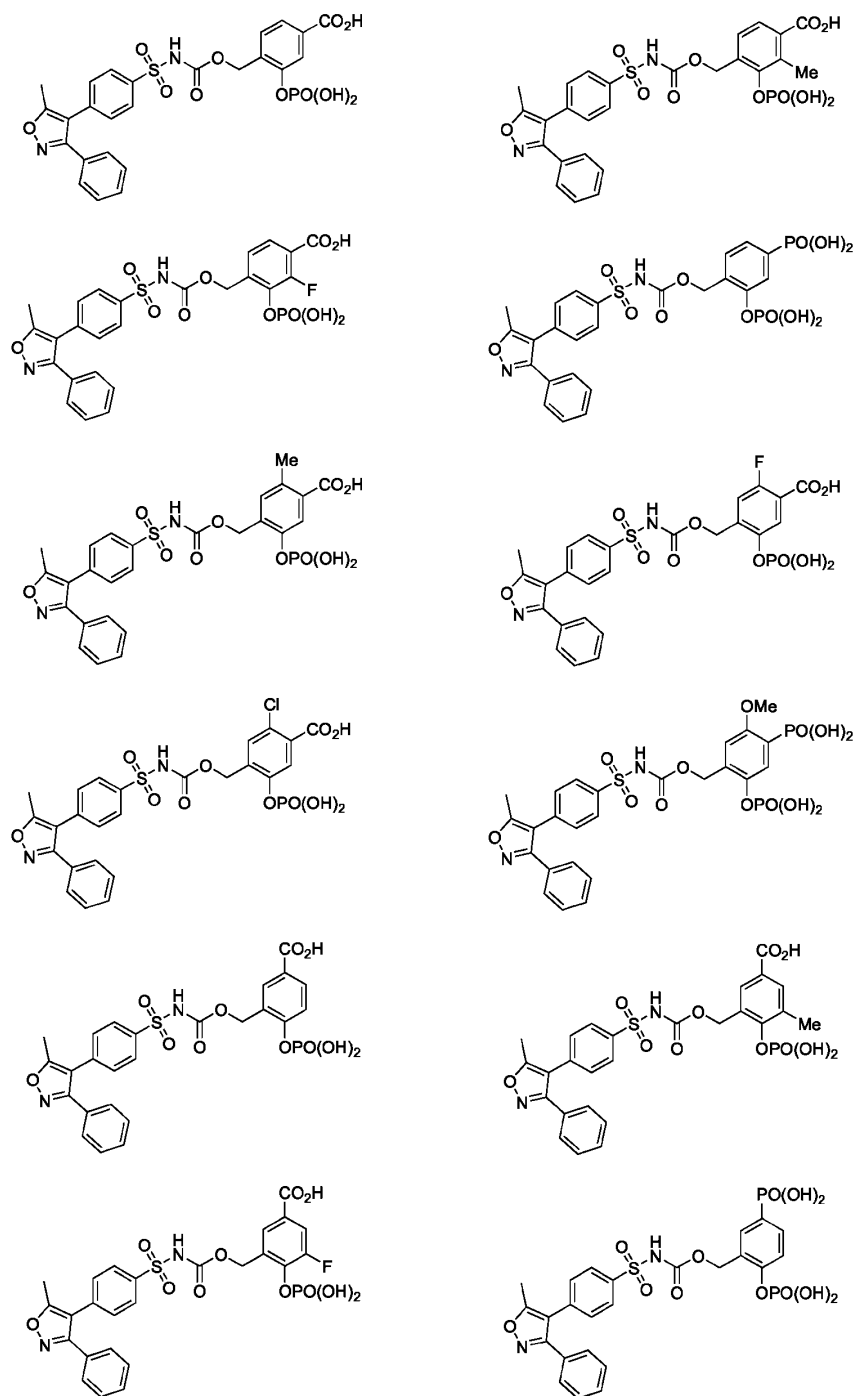


FIG. 50

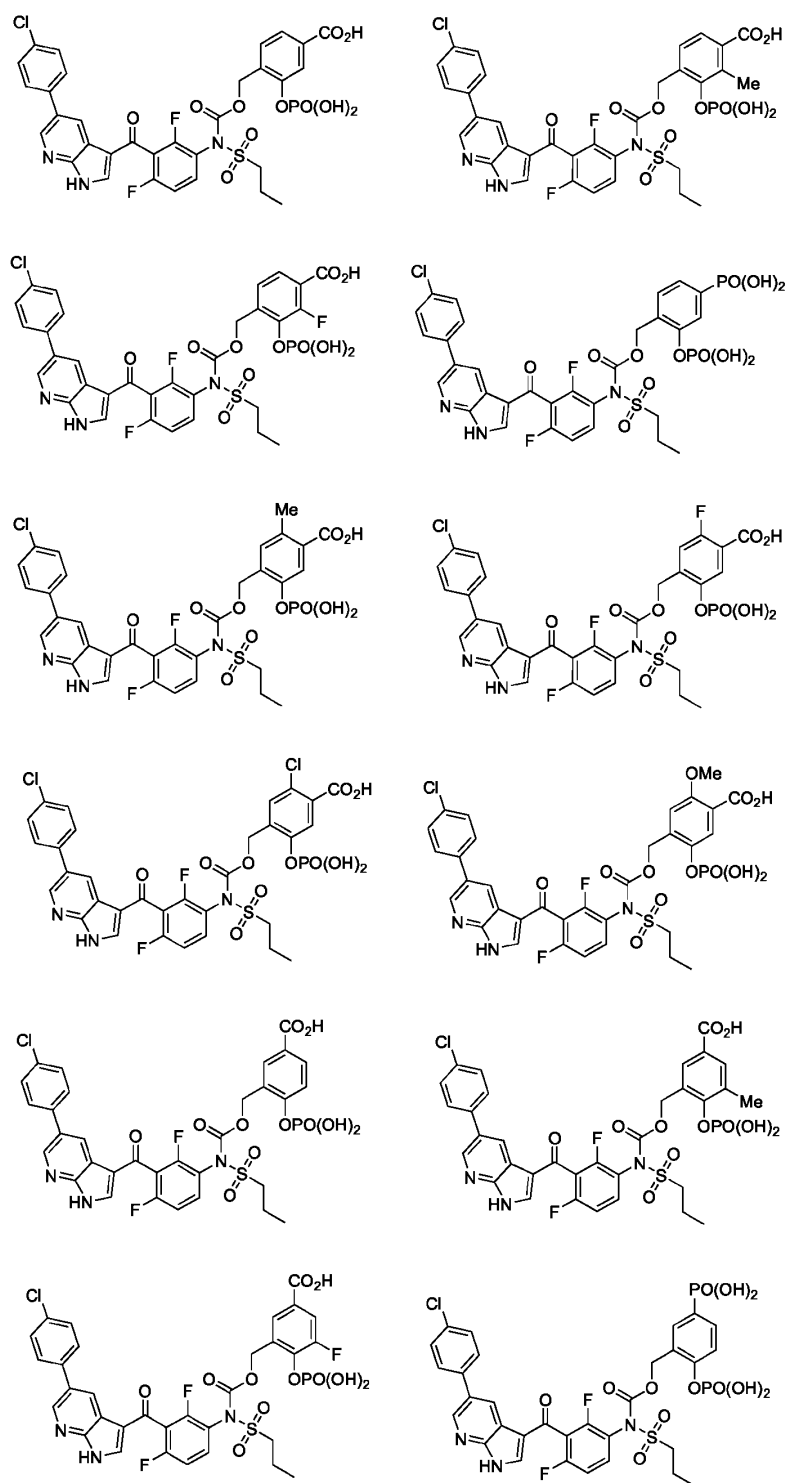


FIG. 51A

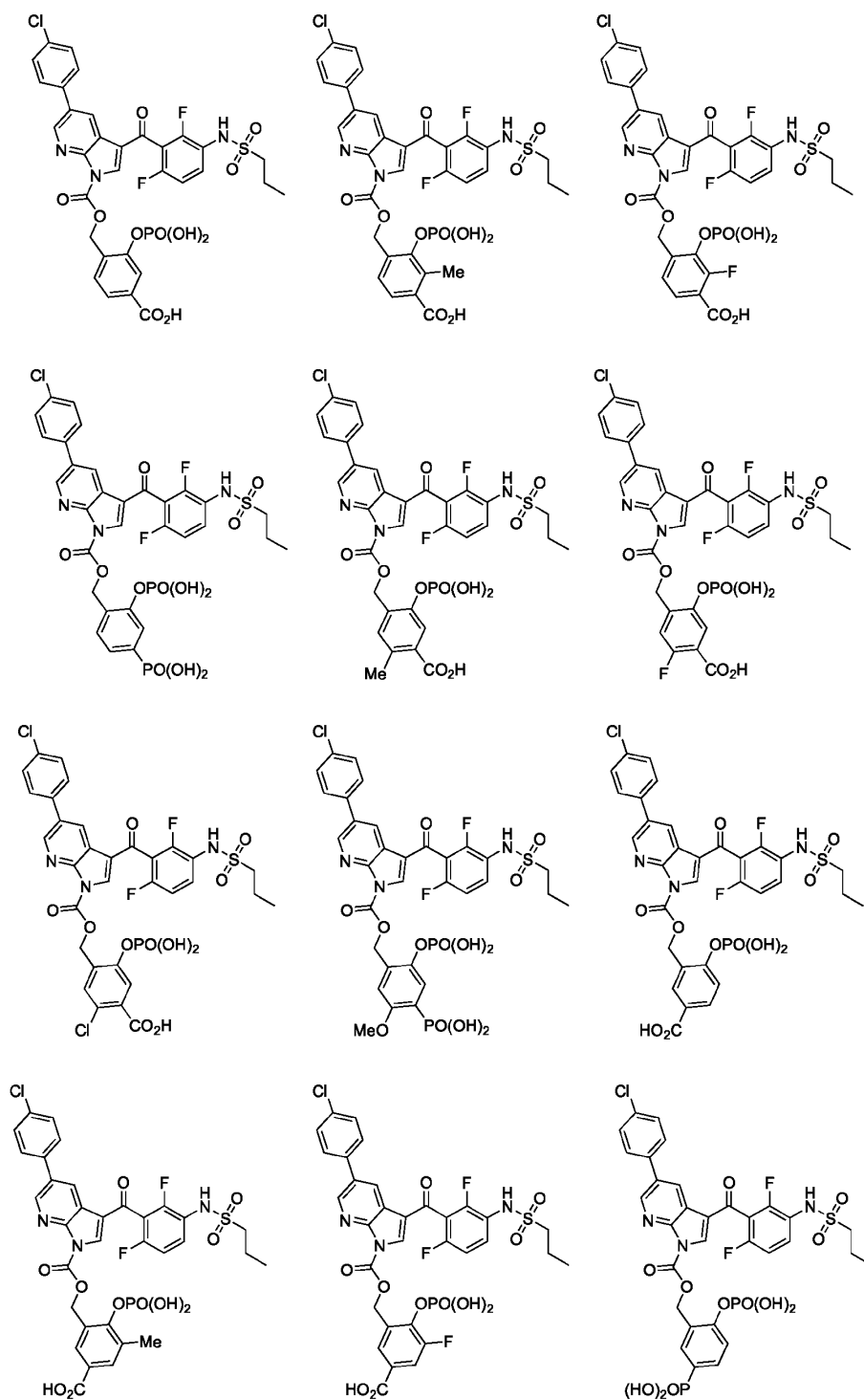
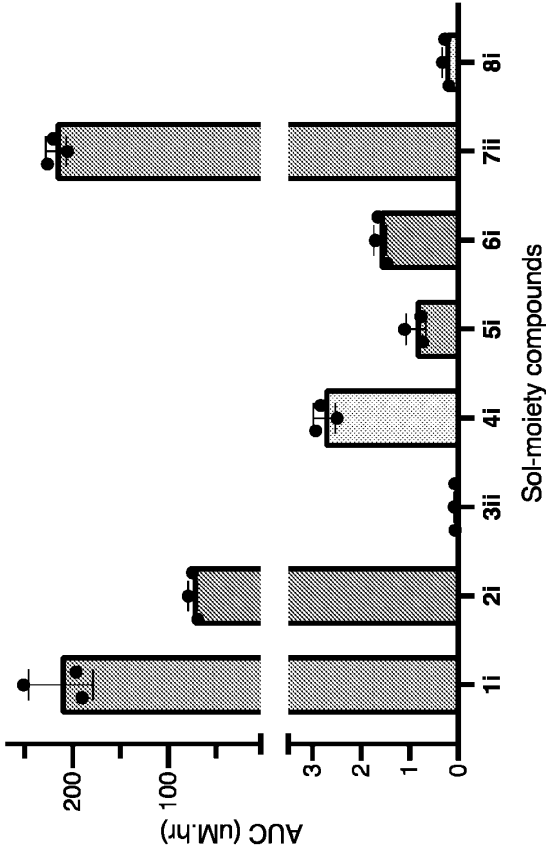


FIG. 51B

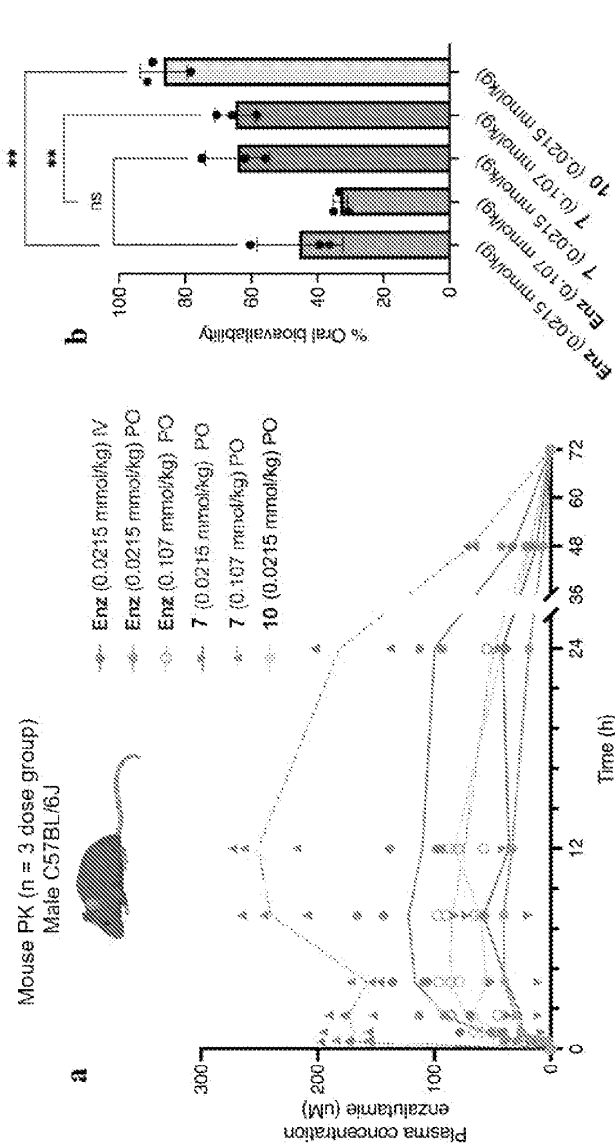
FIG. 53

	7	49	62	41	148	78	155	131	X	Y
Mouse pharmacokinetic study oral dose (nmol/kg)	0.0107	0.0107	0.0107	0.0108	0.0128	0.019	0.0107	0.0041	0.024	0.122
C _{max} (μM)	11.5	8.6	0.02	1.34	0.20	1.89	11.4	0.08	6.05	ND
AUC _{last} (μM•hr) _{0-24 h}	212.7	74.7	0.08	2.75	0.87	1.61	217.5	0.27	3.93	ND

ND = Not detected in plasma samples

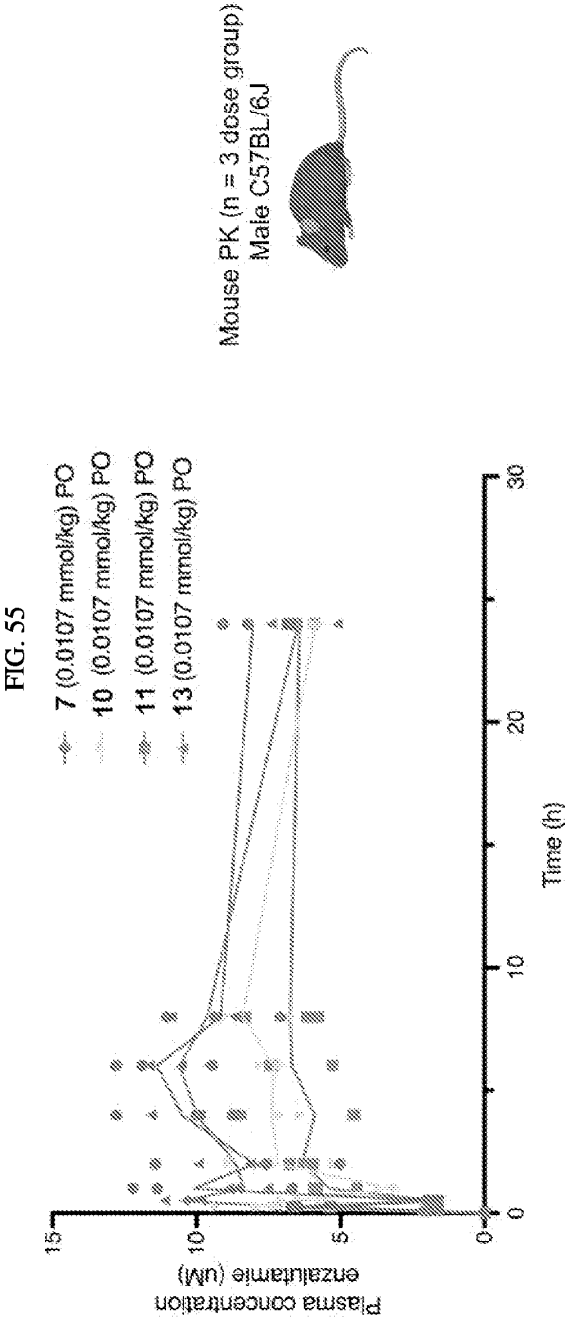


FIGS. 54A-B



Enzalutamide (Enz)					7	10
Dose (mg/kg)	10	10	50		16.9 (10 mg/kg equivalent Enz)	17.25 (10 mg/kg equivalent Enz)
Dose (mmol/kg)	0.0215	0.0215	0.107		0.0215	0.0215
Formulation	10% DMSO	CMC/Tween 80	CMC/Tween 80		Water	Water
Route of administration	IV ^a	Oral	Oral		Oral	Oral
Cmax (nM)	91.1	47.3	149.3		66.3	36.3
Tmax (hr)	6.6	6.6	9.3		13.3	10.6
AUC (µM·hr)	2470	1121	4023		1359	2133

^aRetro-orbital injection. n = 3 mice per dose group. ns = P > 0.05, * P ≤ 0.05, ** P ≤ 0.01, *** P ≤ 0.001

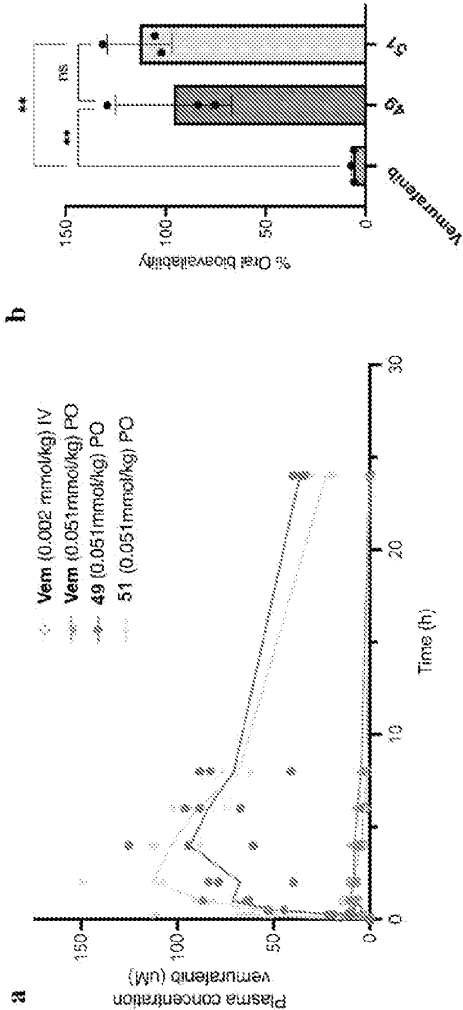


	7 ^b	10	11	13
Hydrolysis rates in ALP solution (pmol/min) ^a	4.16	2.97	3.43	1.81
Caco-2 P _{app} × 1e-6 cm/s (AB)	0.0	0.0	0.0	0.0
Caco-2 P _{app} × 1e-6 cm/s (AB) enzalutamide	11.9	8.9	9.5	8.4
Dose (mg/kg)	8.8	8.8	8.8	8.9
Dose mmol/kg	0.0107	0.0107	0.0107	0.0107
C _{max} (μM)	11.51	9.25	8.14	11.2
T _{max} (hr)	3.67	5.42	6.0	3.5
AUC (μM·hr) _{0-24 h}	212.7	170	153	204

^aHuman placental alkaline phosphatase. ^bData previously shown

FIGS. 56A-B

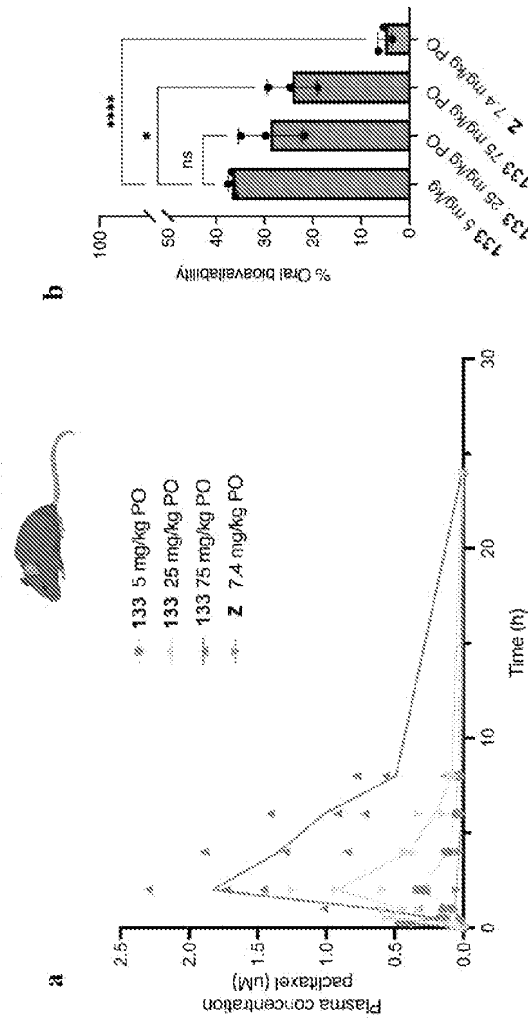
Mouse PK (n = 3 dose group)
Male C57BL/6J



Vemurafenib		49	51
Dose (mg/kg)	1 25	41 ^a	43 ^a
Dose (mmol/kg)	0.002 0.051	0.051	0.051
Formulation	5% DMSO, 5% solutol and 90% saline 20% PEG 400, 5% V/E	Saline	Saline
Route of administration	IV Oral	Oral	Oral
C _{max} (µM)	15.51 11.2	96.35	122
T _{max} (hr)	0.08 0.66	5.33	1.42
t _{1/2} (hr)	2.82 3.35	19.6	9.14
AUC (µM·hr)	50.13 81.02	1200	1418

^a Dosed at 25 mg/kg equivalent of vemurafenib. n = 3 mice per dose group. ns = P > 0.05, ** P = ≤ 0.05, *** P = ≤ 0.001.

FIGS. 57A-B
Mouse PK (n = 3 dose group)
Male C57BL/6J



	Paxitaxel	Z	133*	133	133
Dose	1 mg/kg	7.4 kg (6.27 mg/kg of paxitaxel)	5 mg/kg (3.5 mg/kg of paxitaxel)	25 mg/kg (18 mg/kg of paxitaxel)	75 mg/kg (55 mg/kg of paxitaxel)
Dose (nmol/kg)	0.0012	0.0073	0.004	0.021	0.064
Formulation	DMSO (10%), Tween 80 (10%), water (80%)	saline	saline	saline	saline
Route of administration	IV	Oral	Oral	Oral	Oral
C _{max} (µM)	0.9	0.06	0.3	0.93	1.83
T _{max} (hr)	0.14	1.17	2.0	2.0	2.0
AUC (µM·hr)	0.76 (±0.08)	0.24 (±0.06)	0.98 (±0.02)	3.95 (±0.9)	10.16 (±2.71)

FIGS. 58A-C

